Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende encorafenib i kombination med binimetinib som mulig standardbehandling til ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om omkostningerne ved behandling lægemidlet er rimelige i forhold til lægemidlets kliniske værdi.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	20. februar 2019
Ikrafttrædelsesdato	20. februar 2019
Dokumentnummer	42126
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 20. februar 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Braftovi i kombination med Mektovi
Generisk navn	Encorafenib i kombination med binimetinib
Firma	Pierre Fabre
ATC-kode	L01XE46 L01XE41
Virkningsmekanisme	Encorafenib: BRAF-hæmmer Binimetinib: MEK 1/2-hæmmer
Administration/dosis	Encorafenib 450 mg 1 gang dagligt, oral tabletbehandling Binimetinib 45 mg 2 gange dagligt, oral tabletbehandling
EMA-indikation	Encorafenib i kombination med binimetinib til behandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** encorafenib i kombination med binimetinib som mulig standardbehandling til patienter uden hjernemetastaser med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinjebehandling med en BRAF-MEK-hæmmer.

Medicinrådet **anbefaler** encorafenib i kombination med binimetinib som mulig standardbehandling til patienter uden hjernemetastaser med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600mutation, som er kandidater til andenlinjebehandling med en BRAF-MEK-hæmmer.

Medicinrådet vurderer, at der er et rimeligt forhold mellem den kliniske merværdi af encorafenib i kombination med binimetinib og de forventede omkostninger.

Medicinrådet har besluttet at udarbejde en fælles regional behandlingsvejledning for terapiområdet. Indtil da vurderer Medicinrådet, at encorafenib i kombination med binimetinib kan ligestilles med dabrafenib i kombination med trametinib som første- og andenlinjebehandling til patienter uden hjernemetastaser på baggrund af effekt og bivirkninger. Det anbefales, at regionerne vælger det regime, der er forbundet med de laveste omkostninger.

De kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger:

Hvilken klinisk merværdi tilbyder encorafenib i kombination med binimetinib sammenlignet med dabrafenib i kombination med trametinib til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinjebehandling med en BRAF-MEK-hæmmer?

Hvilken klinisk merværdi tilbyder encorafenib i kombination med binimetinib sammenlignet med dabrafenib i kombination med trametinib til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med en BRAF-MEK-hæmmer?

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende encorafenib i kombination med binimetinib som mulig standardbehandling til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Prognosen for modermærkekræft er generelt god, da de fleste tilfælde opdages tidligt. Forekomst af organmetastaser er dog ensbetydende med en meget dårlig prognose. For stadie IV-patienter var der, baseret på danske upublicerede tal, en femårsoverlevelse på cirka 13 % for alle diagnosticerede med ikke-resektabel melanom i 2012. Prognosen er bedre, hvis der kun er spredning til huden eller til lymfeknuder fjernt fra tumorstedet, sammenlignet med spredning til indre organer. Omkring 50 % af patienterne med ikke-resektabel eller metastatisk modermærkekræft har en BRAF V600-mutation.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Den endelige ansøgning fra Pierre Fabre blev godkendt den 13. november 2018 (se bilag 5). Ansøgningen blev valideret af Medicinrådets sekretariat. Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol (se bilag 6).

Sagsbehandlingstiden fra endelig ansøgning til anbefaling den 20. februar 2019 er 14 uger og 1 dag.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at encorafenib/binimetinib til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinjebehandling med en BRAF-MEK-hæmmer, giver en **ikkedokumenterbar klinisk merværdi** (meget lav evidenskvalitet).

Medicinrådet vurderer, at encorafenib/binimetinib til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med en BRAF-MEK-hæmmer, giver **ingen klinisk merværdi** (meget lav evidenskvalitet).

Medicinrådet har besluttet at udarbejde en fælles regional behandlingsvejledning for terapiområdet. Indtil da vurderer Medicinrådet, at encorafenib i kombination med binimetinib kan ligestilles med dabrafenib i kombination med trametinib som første- og andenlinjebehandling til patienter uden hjernemetastaser på

baggrund af effekt og bivirkninger.

6 Høring

Pierre Fabre har den 31. januar 2019 indsendt et høringssvar. Høringssvaret har ikke medført ændringer i kategoriseringen, men enkelte formuleringer er præciseret i Medicinrådets vurdering af klinisk merværdi for encorafenib i kombination med binimetinib til ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, version 1.1 efter høringssvar.

Høringssvar er vedlagt som bilag 3.

7 Resumé af økonomisk beslutningsgrundlag

Amgros har vurderet de gennemsnitlige meromkostninger pr. patient og budgetkonsekvenserne for regionerne ved brug af encorafenib i kombination med binimetinib i første linje. Amgros' analyseperspektiv er 5 år, og omkostninger relateret til efterfølgende behandlingslinjer er medtaget. Amgros har indgået aftale med Pierre Fabre om indkøb af encorafenib i kombination med binimetinib til en pris, der er lavere end listeprisen (AIP). Amgros' analyser – baseret på aftaleprisen – viser, at behandling med encorafenib i kombination med binimetinib i første linje er forbundet med færre omkostninger pr. patient sammenlignet med den nuværende behandling. På den baggrund vurderer Amgros, at der er et rimeligt forhold mellem klinisk merværdi og omkostninger.

Ansøger har ikke indsendt en sundhedsøkonomisk analyse for andenlinjebehandling, og Amgros har derfor ikke vurderet omkostningerne forbundet med brug af encorafenib/binimetinib i anden linje.

Medicinrådet har vurderet, at encorafenib i kombination med binimetinib klinisk kan ligestilles med dabrafenib i kombination med trametinib i både første og anden linje til patienter uden hjernemetastaser. Medicinrådet anser det derfor ikke for sandsynligt, at en sundhedsøkonomisk analyse for andenlinjebehandling vil få markant anderledes udfald sammenlignet med analysen for førstelinjebehandling.

Budgetkonsekvenserne påvirkes dog, når man også betragter anden linje, idet der i alt forventes at være ca. 105-120 patienter i de to populationer mod 50-60 patienter i første linje alene.

Medicinrådet vurderer, at forholdet mellem omkostningerne og den kliniske merværdi er rimelig ved behandling med encorafenib i kombination med binimetinib i både første og anden linje.

Amgros' beslutningsgrundlag og sundhedsøkonomiske analyse er vedlagt som bilag 1 og 2.

8 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen.

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende modermærkekræft og non-melanom hudkræft

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
Marco Donia Klinisk lektor, afdelingslæge, ph.d.	Lægevidenskabelige Selskaber og udpeget af Region Hovedstaden
Medlemmer	**Udpeget af**
Adam Andrzej Luczak Overlæge	Region Nordjylland
Trine Heide Øllegaard Afdelingslæge, ph.d.	Region Midtjylland
Lars Bastholt Overlæge	Region Syddanmark
Kan ikke udpege	Region Sjælland
Jakob Henriksen 1. reservelæge	Dansk Selskab for Klinisk Farmakologi (DSKF)
Ingen udpegning	Dansk Selskab for Sygehusapoteksledelse (DSS)
Mathilde Skaarup Larsen Overlæge, ph.d.	Dansk Patologiselskab (DPAS)
Lisbet Rosenkrantz Hölmich Klinisk forskningslektor, overlæge, dr.med.	Dansk Selskab for Plastik- og Rekonstruktionskirurgi (DSPR) og Dansk Melanom Gruppe (DMG)
Søren Chrestensen Patient/patientrepræsentant	Danske Patienter
Lene Ottesen Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Jette Østergaard Rathe (projekt- og metodeansvarlig) Pernille Koefod Arrevad (sundhedsvidenskabelig konsulent) Charlotte Wulff Johansen (fagudvalgskoordinator) Tenna Bekker (teamleder) Bettina Fabricius Christensen (informationsspecialist) Jan Odgaard-Jensen (statistiker)

10 Versionslog

Version	Dato	Ændring
1.0	20.02.2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

1. Amgros' beslutningsgrundlag for encorafenib-binimetinib
2. Amgros' sundhedsøkonomiske analyse for encorafenib-binimetinib
3. Høringssvar fra ansøger vedr. encorafenib-binimetinib
4. Medicinrådets vurdering af klinisk merværdi for encorafenib i kombination med binimetinib
5. Ansøgers endelige ansøgning vedr. encorafenib-binimetinib
6. Protokol for Medicinrådets vurdering af klinisk merværdi for encorafenib i kombination med binimetinib

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af encorafenib (Braftovi) i kombination med binimetinib (Mektovi) som mulig standardbehandling til ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	20-02-2019
Firma	Pierre Fabré (ansøger)
Lægemiddel	Encorafenib (Braftovi) + binimetinib (Mektovi)
Indikation	Encorafenib i kombination med binimetinib til behandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation.

Amgros' vurdering

- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for encorafenib (Braftovi) i kombination med binimetinib (Mektovi) som mulig standardbehandling til 1.-linjebehandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation

Ansøger har ikke indsendt en sundhedsøkonomisk analyse, der sammenligner encorafenib (Braftovi) i kombination med binimetinib (Mektovi) med komparator ved 2.-linjebehandling. Amgros kan derfor **ikke vurdere**, om der er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for encorafenib (Braftovi) i kombination med binimetinib (Mektovi) som mulig standardbehandling til 2.-linjebehandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation.

Overordnet konklusion

Medicinrådet har vurderet, at encorafenib (Braftovi) i kombination med binimetinib (Mektovi) sammenlignet med de mulige komparatorer giver:

- **Ikke-dokumenterbar klinisk merværdi** ved 1.-linjebehandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation
- **Ingen klinisk merværdi** ved 2.-linjebehandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation

Behandling med encorafenib (Braftovi) i kombination med binimetinib (Mektovi) er forbundet med omkostningsbesparelser sammenlignet med dabrafenib i kombination med trametinib ved 1.-linjebehandling. Amgros vurderer, at forholdet mellem klinisk merværdi og omkostning er rimeligt.

Amgros har indgået en aftale med Pierre Fabré om indkøb af encorafenib (Braftovi) og binimetinib (Mektovi) til en SAIP, som er lavere end AIP. Konklusionen er baseret på SAIP for encorafenib (Braftovi) og binimetinib (Mektovi).

Andre overvejelser

Amgros har indgået en aftale med ansøger om køb af encorafenib (Braftovi) og binimetinib (Mektovi) til en pris, der er lavere end AIP. Aftalen er gældende fra 20.02.2019 til og med 31.03.2019. Herefter gælder aftalepriser fra et nyt udbud med aftalestart 01.04.2019.

Amgros har vurderet, at der er et rimeligt forhold mellem meromkostninger og den kliniske merværdi ved behandling i 1. linje, da fagudvalget ligestiller encorafenib (Braftovi) i kombination med binimetinib (Mektovi) med dabrafenib i kombination med trametinib i begge linjer, jf. Medicinrådets vurderingsrapport for den kliniske merværdi.

Konklusion for populationen

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
1.-linjebehandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation	Dabrafenib i kombination med trametinib	Ikke-dokumenterbar klinisk merværdi	-	Rimeligt
2.-linjebehandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation	Dabrafenib i kombination med trametinib	Ingen klinisk merværdi	Meget lav evidenskvalitet	Ikke vurderet

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Amgros' afrapportering af omkostnings- og budgetkonsekvensanalyser er baseret på AIP for encorafenib (Braftovi) i kombination med binimetinib (Mektovi). Foretages analyserne på baggrund af SAIP og ikke på baggrund af AIP reduceres de inkrementelle omkostninger, hvilket gør behandling med encorafenib (Braftovi) i kombination med binimetinib (Mektovi) omkostningsbesparende. Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient (AIP)

1.-linjebehandling med encorafenib (Braftovi) i kombination med binimetinib (Mektovi) er forbundet med meromkostninger ubetydelig størrelse sammenlignet med behandling med dabrafenib i kombination med trametinib.

Ansøger har ikke indsendt en sundhedsøkonomisk analyse vedrørende 2.-linjebehandling.

I tabel 2 ses de inkrementelle omkostninger for encorafenib (Braftovi) i kombination med binimetinib (Mektovi) og komparatorer over en tidshorisont på 5 år.

Tabel 2: Gennemsnitlige behandlingsomkostninger for 1.-linjebehandling, DKK, AIP.

	Encorafenib (Braftovi) i kombination med binimetinib (Mektovi)	Dabrafenib i kombination med trametinib	Inkrementelle omkostninger
Lægemiddelomkostninger	3.367.796	3.367.792	4
Efterfølgende behandlinger	1.503.369	1.503.369	-
Hospitalsomkostninger	393.446	393.446	-
Omkostninger til bivirkninger	911	603	308
Totale omkostninger	**5.265.522**	**5.265.210**	**312**

Amgros' afrapportering – Budgetkonsekvenser (AIP)

Amgros vurderer at anbefaling af encorafenib (Braftovi) i kombination med binimetinib (Mektovi) som mulig standardbehandling vil resultere i budgetkonsekvenser ca. 17.000 DKK per år.

ENCORAFENIB (BRAFTOVI) I KOMBINATION MED BINIMETINIB (MEKTOVI)

IKKE-RESEKTABEL ELLER METASTATISK MODERMÆRKEKRÆFT MED BRAF V600 MUTATION

AMGROS

AMGROS 15. januar 2019

OPSUMMERING

Baggrund

Encorafenib (Braftovi) i kombination med binimetinib (Mektovi) er indiceret til behandling af ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation. Det forventes, at ca. 55-60 patienter per år vil kandidere til 2. linje behandling, mens 50-60 patienter vil være potentielle kandidater til 1. linje behandling med den ansøgte indikation i Danmark. Amgros' vurdering tager udgangspunkt i dokumentationen indsendt af Pierre Fabré.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med behandling med ENCO+BINI sammenlignet med behandling med dabrafenib (Tafinlar) i kombination med trametinib (Mekinist) til voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation.

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige inkrementelle omkostninger per patient ved brug af ENCO+BINI sammenlignet med komparator. De inkrementelle omkostninger er angivet i AIP.

I analysen, som Amgros mener er mest sandsynlig, er de gennemsnitlige inkrementelle omkostninger for ENCO+BINI ca. 300 kr. per patient.

Amgros vurderer at budgetkonsekvenserne for regionerne per år ved anbefaling af ENCO+BINI som standardbehandling vil være ca. 17.000 kr. per år.

Konklusion

Amgros kan konkludere, at behandling med encorafenib (Braftovi) i kombination med binimetinib (Mektovi) ikke er forbundet meromkostninger sammenlignet med komparator. Meromkostningerne er i denne analyse udelukkende drevet af omkostninger forbundet med behandling af bivirkninger.

Liste over forkortelser

AIP	Apotekernes indkøbspris
DABRA+TRAM	Dabrafenib (Tafinlar) i kombination med trametinib (Mekinist)
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
ENCO+BINI	Encorafenib (Braftovi) i kombination med binimetinib (Mektovi)
OS	Overall survival
PF	Progressionsfri
PFS	Progressionsfri overlevelse
PP	Post-progression
SAIP	Sygehusapotekets indkøbspris
SPC	Summary of Product Characteristics

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Pierre Fabré
Handelsnavn:	Braftovi i kombination med Mektovi
Generisk navn:	Encorafenib + binimetinib
Indikation:	Encorafenib i kombination med binimetinib til behandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation.
ATC-kode:	L01XE46 + L01XE41

Proces	
Ansøgning modtaget hos Amgros:	13-11-2018
Endelig rapport færdig:	15-01-2019
Sagsbehandlingstid fra endelig ansøgning:	63 dage
Arbejdsgruppe:	**Line Brøns Jensen** Mark Friborg Louise Greve Dal Lianna Christensen Pernille Winther Johansen

Priser

Alle lægemiddelpriser i denne afrapportering er på AIP-niveau. Amgros har ofte aftaler om rabatter på de analyserede lægemidler. Derfor vil analyser på AIP-niveau ikke altid afspejle regionernes faktiske omkostninger til anskaffelse af lægemidlerne. Da rabatterne varierer betragteligt på tværs af lægemidler, vil prisforskellene i afrapporteringen, ikke altid afspejle de faktiske prisforskelle.

Anbefalingerne i Amgros' beslutningsgrundlag, som sendes sammen med denne afrapportering, bygger på regionernes faktiske anskaffelsespriser (SAIP).

1 BAGGRUND

Encorafenib (Braftovi) i kombination med binimetinib (Mektovi), herefter ENCO+BINI, er indiceret til behandling af voksne patienter med ikke-resektabel eller metastaserende modermærkekræft med BRAF V600 mutation. Pierre Fabré (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af ENCO+BINI og har den 13.11.2018 indsendt en ansøgning til Medicinrådet om anbefaling af ENCO+BINI som standardbehandling på danske sygehuse af den nævnte indikation. Som led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de inkrementelle omkostninger forbundet med behandling af voksne patienter med ikke-resektabel eller metastaserende modermærkekræft med BRAF V600 mutation, i form af de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling af ENCO+BINI som standardbehandling på danske sygehuse af den nævnte indikation. I analyserne sammenlignes behandling med ENCO+BINI med behandling med dabrafenib (Tafinlar) i kombination med trametinib (Mekinist), herefter DABRA+TRAM, der er defineret i Medicinrådets protokol som nuværende standardbehandling.

1.2 Patientpopulation

Modermærkekræft er blandt de hyppigste kræftformer i Danmark. Ifølge Dansk Modermærkekræft Gruppes årsrapport blev der i 2016 registreret 2.778 nye tilfælde i Danmark. Sygdommen optræder hovedsageligt hos personer i aldersgruppen 40 til 70 år, men helt unge rammes også.(1)

Prognosen for modermærkekræft i Danmark er god, da de fleste tilfælde opdages tidligt. Internationale tal for 5 års- og 10 års overlevelsen er hhv. stadium IIIA 93 % og 88 %, stadium IIIB 83 % og 77 %, stadium IIIC 69 % og 60 % og for stadium IIID 32 % og 24 %. Prognosen er bedre, hvis der kun er spredning til huden eller til lymfeknuder fjernt fra tumorstedet (M1a), sammenlignet med spredning til indre organer (M1b, M1c eller M1d).(1)

Den primære behandling er operation. Trods operation vil nogle patienter udvikle metastatisk modermærkekræft og være kandidater til medicinsk behandling (ca. 330 nye patienter pr. år). Omkring 40-50 % af disse patienter har en BRAF-mutation. De organer, sygdommen hyppigst metastaserer til, er lymfeknuder, lunger, lever og hjerne, men også metastaser til knogler, knoglemarv, milt og andre organer, samt muskler og bindevæv ses. Forekomst af organmetastaser er generelt ensbetydende med en meget dårlig prognose.(1)

1.3 Behandling med encorafenib (Braftovi) i kombination med binimetinib (Mektovi)

Indikation

ENCO+BINI er indiceret til behandling af ikke-resektabel eller metastaserende modermærkekræft hos voksne med BRAF V600 mutation.

Virkningsmekanisme

Encorafenib er en selektiv hæmmer af BRAF kinasen og hæmmer MAPK-signalvejen hos BRAF V600E, V600D og V600K muterede melanom celler.(2)

Binimetinib er en selektiv hæmmer af MEK1 og MEK2, som aktiverer mitogen aktiveret protein.(2)

Dosering

Oral tablet encorafenib, 450 mg 6 tabletter á 75 mg 1 gang dagligt, i kombination med oral tablet binimetinib, 45 mg 3 tabletter á 15 mg 2 gange dagligt.

1.3.1 Komparator

Medicinrådet har defineret komparator som dabrafenib (Tafinlar) i kombination med trametinib (Mekinist). Komparatoren administreres således:

- Oral tablet dabrafenib, 150 mg á 75 mg 2 gange dagligt, i kombination med oral tablet trametinib, 2 mg 1 tablet dagligt.

1.4 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af behandling med ENCO+BINI sammenlignet med DA-BRA+TRAM for følgende populationer:

- Voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til 1. linje behandling med BRAF-MEK hæmmere.
- Voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til 2. linje behandling med BRAF-MEK hæmmere.

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

I analysen af gennemsnitlige behandlingsomkostninger per patient sammenlignes behandling med ENCO+BINI med behandling med DABRA+TRAM til voksne patienter med ikke-resektabel eller metastatisk modermærke-kræft med BRAF V600 mutation.

2.1 Model, metode og forudsætninger

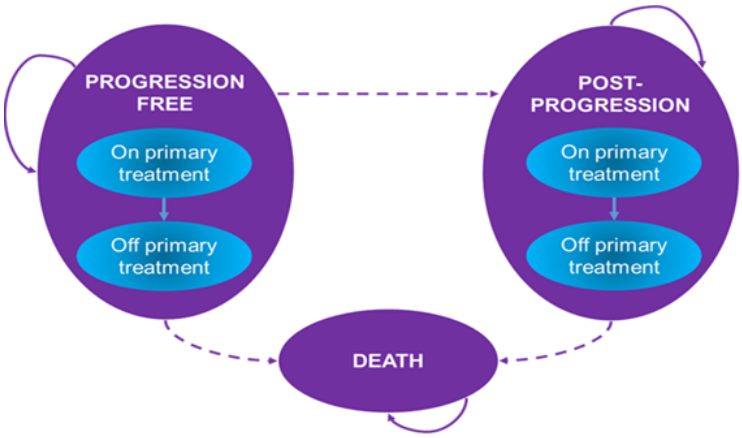
2.1.1 Modelbeskrivelse

Ansøger har indsendt en model for behandling af patienter i den nævnte population for 1. linje behandling, men ikke for 2. linje behandling grundet manglende data.

Patienter i modellen allokeres til behandling med enten ENCO+BINI eller DABRA+TRAM, hvorefter de overgår til stadiet "Progressionsfri" (PF). Ved sygdomstilbagefald bevæger patienterne sig til stadiet "Post-progression" (PP) og ved død til stadiet "Død". Transitionen mellem stadierne er bestemt ud fra overlevelseskurver fra COLUMBUS-studiet.(2,3) Således er sandsynligheden for at befinde sig i PF lig med sandsynligheden for progressionsfri overlevelse (PFS). Sandsynligheden for at befinde sig i PP er lig med sandsynligheden for overlevelse (OS) minus PFS. Og sandsynligheden for død er lig med 1-OS.

I hvert stadie, hvor patienterne stadig er i live (PF og PP), benytter ansøger time-to-discontinuation til at estimere, hvor stor en andel af patienterne der i PF og PP stadig er i behandling og hvor mange der er stoppet på behandlingen. Ansøger antager desuden, at behandlingslængden for ENCO+BINI og DABRA+TRAM vil være ens. Behandlingslængden er angivet som begrænset gennemsnit indenfor studieperioden på 26 måneder.

Figur 1: Modelstruktur



For efterfølgende behandlingslinjer har ansøger estimeret behandlingslængder baseret på input fra to danske kliniske eksperter. Disse antager, at alle BRAF-inhibitorer vil have en behandlingslængde på 6 måneder, mens immunonkologiske behandlinger og kemoterapi vil have behandlingslængder på henholdsvis 7,7 måneder og 3 måneder uanset, hvilket lægemiddel der anvendes i den angivne klasse.

Behandlingslængden for *best supportive care* estimeres at være 4 måneder baseret på et europæisk studie, der undersøgte behandlingen af patienter med metastatisk modermærkekræft.(4) *Best supportive care* er defineret som en række konsultationer, indlæggelser, hjemmepleje og procedurer.

Amgros' vurdering

Amgros har bedt regionerne udpege klinikere med ekspertise indenfor det relevante område, og bedt de valgte klinikere om at validere ansøgers grundlæggende antagelser og estimater. Regionerne udpegede tre klinikere, der svarede på spørgsmål angående ansøgers modelstruktur og estimater. På baggrund af deres svar har Amgros

ikke fundet grund til at ændre i den grundlæggende modelstruktur, men ændrer få estimater forbundet med behandling af bivirkninger (dette er beskrevet nærmere i afsnit 2.1.3 Omkostninger under "Omkostninger til bivirkninger").

Ansøger estimerer behandlingslængden for ENCO+BINI og DABRA+TRAM baseret på studiedata fra COLUMBUS-studiet.(2) Ved studiets afslutning, var der stadig en stor del af patienterne, der stadig var i behandling, hvorfor Amgros vurderer, at det ikke er acceptabelt at benytte begrænset gennemsnitsværdi for behandlingslængden. Ansøger har indsendt en model med mulighed for at vælge forskellige datagrundlag for behandlingslængden. Heriblandt er det muligt at benytte ekstrapolerede data baseret på Kaplan-Meier-kurver fra COLUMBUS-studiet.(2) Benyttes den estimerede behandlingslængde på baggrund af disse data, er den gennemsnitlige behandlingslængde markant længere end ved brug af den begrænsede gennemsnitlige behandlingslængde fundet i studiet. Amgros benytter derfor disse ekstrapolerede data til at estimere behandlingslængden i Amgros' hovedanalyse.

Amgros accepterer ansøgers antagelser om ens patientforløb for ENCO+BINI og DABRA+TRAM. Amgros udarbejder en ny hovedanalyse, hvor der benyttes ekstrapolerede data til bestemmelse af behandlingslængde.

2.1.2 Analyseperspektiv

Analysen anvender et begrænset samfundsperspektiv. Tidshorisonten i analysen er 26 måneder, svarende til længst muligt opfølgningstid i COLUMBUS-studiet.(3) Analysen anvender en cykluslængde på en måned. Omkostninger er diskonteret med en faktor på 4%.

Amgros' vurdering

Analysens perspektiv er i tråd med Amgros' retningslinjer, Jf. Amgros Metodevejledning om, hvad der må inkluderes i en økonomisk analyse.

Ansøger har medsendt ekstrapoleret data ud fra Kaplan-Meier-kurver i COLUMBUS-studiet.(2) Denne ekstrapolering viser den gennemsnitlige behandlingslængde som værende markant længere end ved brug af den begrænsede gennemsnitlige behandlingslængde fundet i studiet. Da den estimerede gennemsnitlige behandlingslængde er længere end tidshorisonten på 26 måneder, ændrer Amgros tidshorisonten til 5 år, så alle relevante omkostninger relateret til behandlingen og efterfølgende behandlingslinjer medregnes.

Amgros godtager analysens perspektiv, men ændrer tidshorisonten fra 26 måneder til 5 år.

2.1.3 Omkostninger

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen.

Lægemiddelomkostninger

Ansøger har anvendt de anbefalede doser fra SPC'et for hvert lægemiddel, der er inkluderet i analysen.(5–7) Alle anvendte lægemiddelpriser er angivet i AIP.

Tabel 1 illustrerer de lægemiddelpriser, som anvendes i analysen.

Tabel 1 Anvendte lægemiddelpriser, AIP (juli 2018)

Behandling	Styrke	Pakningsstørrelse (styk)	AIP per pakke (DKK)	Lægemiddelomkostning per måned (DKK)
Binimetinib (Mektovi)	15 mg	84	21.471	46.648
Encorafenib (Braftovi)	75 mg	42	11.960	51.969
Trametinib (Mekinist)	2 mg	30	46.010	46.649
Dabrafenib (Tafinlar)	75 mg	120	51.256	51.968
Temozolomide (Temozolomide "Accord")	100 mg	5	155	5.437
Pembrolizumab (Keytruda®)	25 mg	4	24.937	58.100
Ipilimumab (Yervoy®)	5 mg	40	113.297	197.980
Nivolumab (Opdivo)	10 mg	24	24.349	53.185
Aldesleukin (Proleukin®)	1,1 mg	1	1.297	47.920

Administrations- og monitoreringsomkostninger

Ansøger har estimeret ressourceforbrug og enhedsomkostninger knyttet til administration af lægemidlerne. For oralt administrerede lægemidler antager ansøger, at sygehusapoteket benytter 12 minutters arbejdstid på at håndtere udlevering af lægemidlerne. For intravenøst administrerede lægemidler har ansøger estimeret en administrationsomkostning baseret på antallet af infusioner. Det antages, at subkutane lægemidler administreres af patienten selv. Derfor antager ansøger, at omkostningen forbundet med administration af subkutane lægemidler svarer til omkostningen forbundet med orale lægemidler.

Ansøger antager også, at alle patienter ved behandlingsstart bliver CT-scannet for hjernemetastaser uanset behandlingsalternativ. Omkostningen forbundet med denne scanning er derfor også inkluderet.

Ansøger har bedt to danske kliniske eksperter om at estimere omkostninger forbundet med monitorering af sygdom under behandling. Disse omkostninger er inkluderet for begge behandlingsalternativer og antages at være ens.

Omkostninger til bivirkninger

Ansøger har inkluderet omkostninger forbundet med behandling af grad 3-4 bivirkninger med frekvens >5% fra COLUMBUS-studiet samt COMBI-V- og COMBI-D-studierne.(2,3,8) I tabel 2 ses bivirkningsfrekvensen for hver behandling.

Tabel 2 Frekvens af bivirkninger

Bivirkning	Encorafenib + binimetinib	Dabrafenib + trametinib
Hypertension	5.2%	11.8%
Pyrexi	3.6%	5.4%
Blod CK stigning	6.8%	0.0%
GGT stigning	9.4%	3.4%
ALT stigning	5.2%	2.5%

Ansøger har spurgt danske kliniske eksperter om deres vurdering af bivirkningsbehandlingen. De vurderer, at nogle patienter vil kræve indlæggelse ved behandling af bivirkninger. I tabel 3 ses omkostningerne forbundet med behandling af hver bivirkning, inkluderet fordelingen af ambulante og indlæggelseskrævende behandlinger.

Tabel 3 Enhedsomkostninger forbundet med bivirkninger, kr., DRG-takster

Bivirkning	Ambulant enheds-omkostning per event (DKK)	Indlagt enhedsom-kostning per event (DKK)	Andel, der kræver indlæggelse	Total omkostning per event (DKK)
Hypertension	2.609	40.045	0,0%	2.609
Pyrexi	2.609	16.613	0,0%	2.609
Blod CK stigning	4.143	5.935	15,4%	4.419
GGT stigning	2.609	18.910	0,0%	2.609
ALT stigning	2.609	18.910	0,0%	2.609

Amgros' vurdering

Doseringen af lægemidlerne er i tråd med lægemidlernes SPC'er.

Amgros har bedt regionerne udpege klinikere med ekspertise indenfor det relevante område, og bedt de valgte klinikere om at validere ansøgers grundlæggende antagelser og estimater. Regionerne udpegede 3 klinikere, der svarede på spørgsmål angående ansøgers modelstruktur og estimater. De udpegede kliniske eksperter vurderede, at ansøgers estimater overordnet set var acceptable. Dog blev det nævnt, at andelen af patienter, der kræver indlæggelse grundet feber nok ikke ville være 0%, som ansøger antager.

Amgros accepterer de inkluderede omkostninger, men inkluderer en følsomhedsanalyse på andelen af patienter med indlæggelseskrævende grad 3+ feber.

2.2 Følsomhedsanalyser

Ansøger har ikke udarbejdet følsomhedsanalyser for omkostningsanalysen.

Amgros' vurdering

Efter samtale med udpegede kliniske eksperter, er det vurderet, at andelen af patienter, der oplever grad 3+ indlæggelseskrævende feber kunne undersøges ved frekvens på 15%, 50% og 100% for at udelukke potentiel infektion. Dette har dog ubetydelig indflydelse på det samlede resultat, hvorfor resultaterne af disse ændringer ikke vises her.

Derudover er behandlingslængderne for efterfølgende behandling behæftet med store usikkerheder. Da disse antages at være ens for ENCO+BINI og DABRA+TRAM undersøges dette dog ikke i en følsomhedsanalyse, da det ikke vil have betydning for det samlede resultat.

3 RESULTATER

3.1 Ansøgers hovedanalyse

Ansøgers hovedanalyse resulterer i gennemsnitlige meromkostninger per patient på ca. 900 kr. for ENCO+BINI sammenlignet med DABRA+TRAM.

Resultaterne fra ansøgers hovedanalyse præsenteres i tabel 4.

Tabel 4 Resultat af ansøgers hovedanalyse, gns. omkostninger per patient, DKK, AIP

	Encorafenib + binimetinib	Dabrafenib + trametinib	Inkrementelle omkostninger
Lægemiddelomkostninger	2.626.846	2.626.844	3
Efterfølgende behandlinger	4.721	4.721	
Hospitalsomkostninger	284.713	284.713	-
Omkostninger til bivirkninger	2.595	1.717	878
Totale omkostninger	**2.918.876**	**2.917.995**	**881**

3.2 Amgros' hovedanalyse

3.2.1 Antagelser i Amgros hovedanalyse

Baseret på Amgros' kritiske vurdering af den tilsendte model, har Amgros udarbejdet sin egen hovedanalyse. Forudsætningerne er som i ansøgers analyse, bortset fra følgende:

- *Amgros benytter ekstrapolerede data til estimering af behandlingslængden. Denne bliver således markant længere end ansøgers estimerede behandlingslængde på 15,16 måneder.*
- *Amgros ændrer tidshorisonten til 5 år.*

Amgros' analyse resulterer i gennemsnitlige meromkostninger per patient på ca. 300 kr. for ENCO+BINI sammenlignet med DABRA+TRAM.

Meromkostningerne drives udelukkende af bivirkningsfrekvenserne.

Resultaterne fra Amgros hovedanalyse præsenteres herunder i tabel 5.

Tabel 5 Resultat af Amgros' hovedanalyse, gns. omkostninger per patient, DKK, AIP

	Encorafenib + binimetinib	Dabrafenib + trametinib	Inkrementelle omkostninger
Lægemiddelomkostninger	3.367.796	3.367.792	4
Efterfølgende behandlinger	1.503.369	1.503.369	-
Hospitalsomkostninger	393.446	393.446	-
Omkostninger til bivirkninger	911	603	308
Totale omkostninger	**5.265.522**	**5.265.210**	**312**

4 BUDGETKONSEKVENSER

Budgetkonsekvenserne per år er baseret på antagelsen om, at ENCO+BINI vil blive anbefalet som standardbehandling. Man ser derfor på to scenarier:

- ENCO+BINI bliver anbefalet som standardbehandling af Medicinrådet til indikationen, som denne analyse omhandler.
- ENCO+BINI bliver ikke anbefalet som standardbehandling.

Budgetkonsekvenserne bliver differencen mellem budgetkonsekvenserne i de to scenarier.

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Medicinrådet angiver i protokollen for vurdering af den kliniske merværdi af ENCO+BINI, at ca. 50-60 patienter kandiderer til 1. linje behandling med BRAF-kinasehæmmere i kombination med en MEK1 eller MEK2-hæmmer. For 2. linje behandling estimerer fagudvalget, at omkring 55-60 patienter vil være kandidater til behandlingen.

Ansøger har estimeret patientantallet ved hjælp af udregninger baseret på epidemiologiske data og estimater fra danske kliniske eksperter.

Ansøgers estimerede patientantal er vist i tabel 6.

Tabel 6 Ansøgers estimat af antal patienter

	År 1	År 2	År 3	År 4	År 5
ENCO+BINI anbefales					
ENCO+BINI	117	121	125	130	135
DABRA+TRAM	0	0	0	0	0
ENCO+BINI anbefales ikke					
ENCO+BINI	0	0	0	0	0
DABRA+TRAM	117	121	125	130	135

Amgros' vurdering af estimeret patientantal

Amgros vurderer, at ansøgers estimerede patientantal er en smule højt sammenlignet med Medicinrådets vurdering af antallet af patienter, der kandiderer til behandlingen i 1. linje fra protokollen.

Amgros reducerer patientantallet i Amgros' budgetkonsekvensanalyse, så det svarer til patientantallet nævnt i Medicinrådets protokol for vurdering af den kliniske merværdi.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen.

Med de indlagte antagelser estimerer ansøger, at anvendelse af ENCO+BINI vil resultere i budgetkonsekvenser på ca. 500.000 kr. ved år 5, når der opnås ligevægt.

Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 7.

Tabel 7 Ansøgers hovedanalyse for totale budgetkonsekvenser, kr., diskonterede tal, baseret på AIP.

	År 1	År 2	År 3	År 4	År 5
ENCO+BINI anbefales	153.174.152	298.889.760	582.130.589	581.737.610	579.925.905
ENCO+BINI anbefales ikke	153.137.878	298.853.634	582.094.457	581.222.231	579.500.144
Totale budgetkonsekvenser	**36.274**	**36.126**	**36.133**	**515.379**	**425.762**

4.2 Amgros' estimat af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- *Omkostningerne fra Amgros' hovedanalyse anvendes*
- *Patientantallet sættes til 55 patienter per år*
- *Der benyttes ikke-diskonterede tal jf. Amgros' metodevejledning*

Med de indlagte antagelser estimerer Amgros, at anvendelse af ENCO+BINI vil resultere i budgetkonsekvenser på ca. 17.000 kr. per år.

Amgros' estimat af budgetkonsekvenserne fremgår af tabel 8.

Tabel 8 Amgros' hovedanalyse for totale budgetkonsekvenser, DKK, ikke-diskonterede tal, baseret på AIP.

	År 1	År 2	År 3	År 4	År 5
ENCO+BINI anbefales	71.885.699	143.590.498	288.164.855	289.603.737	289.603.737
ENCO+BINI anbefales ikke	71.868.676	143.573.409	288.147.710	289.586.592	289.586.592
Totale budgetkonsekvenser	**17.024**	**17.090**	**17.145**	**17.145**	**17.145**

5 DISKUSSION

Ansøger vurderer, at behandling med ENCO+BINI er forbundet med meget begrænsede meromkostninger sammenlignet med DABRA+TRAM.

Meromkostningerne er primært drevet af bivirkningsfrekvenserne for de to behandlinger, samt behandlingen af de forekommende bivirkninger, eftersom alt andet i analysen antages at være lige mellem de to behandlinger. Dog har omkostningerne forbundet med behandling af bivirkninger ubetydelig indflydelse på det samlede resultat.

6 REFERENCER

1. Medicinrådet. Protokol for vurdering af den kliniske merværdi af encorafenib i kombination med binimetinib til ikke-resektabel eller metastatisk modermærke- kræft med BRAF V600 mutation. 2018;1–14.
2. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol [Internet]. 2018;18(6):1470–2045. Available from: http://dx.doi.org/10.1016/S1470-2045(18)30142-6
3. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol [Internet]. 2018;19(10):1315–27. Available from: http://dx.doi.org/10.1016/S1470-2045(18)30497-2
4. McKendrick J, Gijsen M, Quinn C, Barber B, Zhao Z. Estimating healthcare resource use associated with the treatment of metastatic melanoma in eight countries. J Med Econ [Internet]. 2016;19(6):587–95. Available from: http://www.tandfonline.com/doi/full/10.3111/13696998.2016.1148043
5. EMA. Assessment report Braftovi. Rep ARZ. 2018;44(June):1–91.
6. Ema. Assessment report Mektovi. 2012;44(June):1–91.
7. Trametinib M, Dabrafenib T. Mekinist, INN: trametinib. 2015;44(September).
8. Long G V., Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol Off J Eur Soc Med Oncol. 2017;28(7):1631–9.

AMGROS

REGIONERNES
LÆGEMIDDELORGANISATION

AMGROS I/S
DAMPFÆRGEVEJ 27-29
2100 KØBENHAVN Ø

TLF: 8871 3000
WWW.AMGROS.DK

Pierre Fabre Ltd Response - 30 January 2019

Draft: Medicine Council's Assessment of Clinical Added Value for Encorafenib in Combination With Binimetinib for the Treatment of Nonresectable or Metastatic Melanoma with BRAF V600 Mutation

Comment no.	Page Number/Section	Comment
1	Page 1, Medicine Council's Conclusion on Clinical Added Value	Pierre Fabre Ltd, recognise that the methods in the assessment handbook have been applied, but are disappointed that the Medicine Council: • Do not consider encorafenib in combination with binimetinib to provide added clinical value for the treatment of nonresectable or metastatic melanoma with BRAF V600 mutation. • Consider the quality of the evidence to be '*very low'* These statements do not accurately reflect the robustness of the pivotal clinical trial (the COLUMBUS trial) nor the provision of both a Bucher and naïve indirect treatment comparison comparing, in the absence of a direct head-to-head trial, encorafenib in combination with binimetinib (Enco+Bini 450) versus dabrafenib in combination with trametinib (Dabra+Tram). <u>COLUMBUS Trial</u> The COLUMBUS trial is an international, randomised, open-label, phase III trial designed to assess the clinical effectiveness of Enco+Bini 450 compared with vemurafenib and compared with Enco 300 in 577 patients with advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma. The COLUMBUS trial was of good quality and was well-conducted, with blinded independent review of PFS outcomes and collection of HRQoL data. <u>Comparative Evidence</u> In the absence of direct evidence comparing treatment with Enco+Bini 450 versus Dabra+Tram both a Bucher analysis and naïve indirect treatment comparison were provided supporting at least equivalent efficacy.

		Furthermore the statement that encorafenib in combination with binimetinib does not provide clinical value contradicts a number of statements made in the report including:
		• Page 17
		  ○ *'Based on the qualitative review, the specialist committee considers that the side effect profiles between the drugs differ significantly in relation to fever, cardiovascular and gastrointestinal side effects, which should be included in the specific clinical assessment.'*
		• Page 21
		  ○ *'Based on an ITC, the expert committee assesses that encorafenib/binimetinib has at least the same effect as dabrafenib/trametinib.*
		  ○ *The committee notes that the side effect profile is different between the drugs. Based on the data basis, the expert committee cannot say whether one drug is preferable to another.*'
		
		.
		
		We would ask the Medicine Council to give due consideration to the following points in order to ensure that the final report does not contain any factual inaccuracies, whilst also clarifying current statements that currently may be open to misinterpretation by external parties on publication.

2	Page 6, Section 2 Current Treatment	**Clarification** It should be made clear that the following patient characteristics identifying patients with BRAF mutation for first-line treatment with a BRAF/MEK inhibitor are specific to Denmark and do not reflect international guidelines: • *'Symptomatic brain metastases* • *Lactate dehydrogenase LDH> ULN * 2 (upper normal limit)* • *High tumor burden* • *Fast-growing disease* • *Symptomatic disease* *or* • *Relative contraindications to immunotherapy (e.g., treatment-requiring autoimmune disease)'* The current ESMO guidelines recommend the use of a BRAF/MEK inhibitor first- or second line in patients with BRAF-mutant metastatic melanoma and make no conclusive reference to specific characteristics, including those listed above. This approach is also reflected in other national guidelines.
3	Page 6, Section 2 Current Treatment	**Clarification** The statement '*Patients treated with BRAF-MEK1/2 second line inhibitor after checkpoint inhibitors do not have the same characteristics as first-line treatment candidates'* requires clarification as to how they are different and also that any characteristics listed are specific to treatment guidelines in Denmark.

4	Page 8, Section 5 Clinical Question1	**Clarification** While it is correct to state that Pierre Fabre did not provide clinical trial information on patients with the characteristics listed in Section 2 of the report it is important to note that, as stated above in comment 2, the requirement for these characteristics prior to receiving a BRAF/MEK inhibitor is specific to Denmark. The COLUMBUS trial population reflects the broad EU population and consequently the patient population eligible to receive treatment with a BRAF/MEK inhibitor as per the ESMO Clinical Practice Guideline. The trial was not powered to detect differences for any country specific populations.
5	Page 9, Section 5 Assessment of Data	**Clarification** The following statement fails to make reference to the fact that PFS estimates from COLUMBUS for Enco+Bini 450 by investigator assessment and BIRC were seen to be similar. Overall, this suggests that any potential impact of blinding on the PFS outcome may be minimal: *'Both included studies of the intervention and comparator are unblinded and there is therefore a risk of bias. The efficacy goal of the COLUMBUS study has been assessed by a blinded independent review committee (BIRC), whereas the efficacy goals of the COMBI-v study are investigator-assessed. This is emphasized in the assessment of the quality of evidence.'*
6	Page 10, Section 6.2, Conclusion Clinical Question 2	**Clarification** We disagree with the conclusion that the Bucher comparison and naïve ITC provide '*very low quality evidence'*. In the absence of any direct head to head data this is the only way the Enco/Bini 450 and Dabra/Tram can be compared. The results of the two approaches support, at a minimum, comparable efficacy however, it is important to note that the magnitude of effect seen in naïve indirect comparison along with the consistent numerical benefit seen with the Bucher comparison suggest Enco/Bini 450 is more effective.

7	Page 11, Section 6.2.1 COLUMBUS (Encorafenib/Binimetinib Versus Vemurafenib) [8.9]	**Clarification** In the paragraph starting '*The primary endpoint of the study….*' ORR is stated as representing '*objective response rate'* whilst earlier in the document it is stating a representing '*overall response rate'*. It should be made clear that within the report both terms are the same.
8	Pages 12, Section 6.2.1 COMBI-V (Dabrafenib/Trametinib Versus Vemurafenib) [10]	**Factual Inaccuracy** Please note that in relation to the below statement, information on subsequent treatments was not made clear to Pierre Fabre and as such the Medicines Council's conclusion is factually inaccurate. Based on the information provided below, we would request that statement below is updated to ensure factual accuracy. *'The expert committee is aware that there is a difference in the calendar time of the two studies' inclusion periods (COLUMBUS and COMBI-V). The available options for treatment by progression have changed over a short period of ipilimumab, which became available in several countries in 2012 and pembrolizumab, which became available from 2014 through EAP (Extensible Authentication Protocol) and later with an EMA approval in 2015. may have an impact on a possible cross-over effect on survival. The COLUMBUS study included patients from December 2013 to April 2015 and the COMBI-V study included patients from June 2012 to October 2013.'* Information **is** however available on use of post-trial immunotherapy. Data presented at ASCO in June 2018 demonstrate that in COLUMBUS the use of post-trial immunotherapy was consistent with other published pivotal trials of BRAF and MEK-inhibitors in *BRAF*-mutant advanced melanoma .In addition, the use of subsequent immunotherapies was consistent across treatment groups indicating that these subsequent treatments are unlikely to have contributed to the observed differences in survival. The data presented also confirmed that the performance of vemurafenib in COLUMBUS was

		consistent with historical data for ORR, PFS, and OS further supporting the robustness of the COLOMBUS study.
9	Page 3, Section 6.2.1 COMBI-MB (Dabrafenib/Trametinib) in Patient Population with Brain Metastases [26]/ Population	**Clarification** The following statement is misleading: *'However, in both studies, the patient population differs from the relevant Danish patient population, which is typically patients who progress after treatment with a checkpoint inhibitor in the first line and where PS is thus significantly worse.'* The sentence fails to acknowledge that the COLOMBUS and COMBI-V studies were initiated prior to the availability of checkpoint inhibitors and at the time of initiation the study trial populations would have reflected the Danish patient population in terms of previous treatment(s).
10	Page 14, Section 6.2.2 Overall Survival (OS) (Critical)	**Clarification** The following statement fails to acknowledge that the information required was not clearly requested from Pierre Fabre: *'The expert committee acknowledges that no information has been given on the treatment the patients in the study have received after progression; therefore, a possible cross-over effect cannot be ruled out*.' As stated above in comment 8, data on subsequent treatments is available for COLOMBUS and was presented at ASCO in June 2018. Pierre Fabre provided data on subsequent treatment to the Medicine Council in the EPAR page 75, but this was not provided in the report as this was not an outcome in the protocol. This information and additional data about subsequent treatment and crossover could have been provided to the Medicine Council but was not clearly requested. In summary in COLUMBUS the use of post-trial immunotherapy was consistent with other published pivotal trials of BRAF and MEK-inhibitors

11	Page 21, Section 6.2.4 Clinical Issue Conclusion	**Clarification** In order to provide a report which avoids any reader misinterpretation, reflects the data available and to be in line with assessment reports presented by other European authorities we would request the following bullets should be included in the conclusion on page 1 of the report • *'Based on an ITC, the expert committee assesses that encorafenib/binimetinib has at least the same effect as dabrafenib/trametinib.* • *The committee notes that the side effect profile is different between the drugs. Based on the data basis, the expert committee cannot say whether one drug is preferable to another.'*
12	Page 21, Section 6.2.4 Clinical Issue Conclusion 2	**Clarification** The following point along with previous points relating to the clinical data on patients with brain metastases treated with Dabra/Tram should specify which clinical endpoints were considered. *'Clinical data are available to support the treatment of patients with dabrafenib/ trametinib brain metastases [26]. That is used in Danish clinical practice for patients with symptomatic brain metastases.'*
13	Page 21, Section 7 Other Considerations	**Clarification** In addition to the considerations currently listed in this section the point that Enco/Bini 450 can be stored at room temperature while Dabra/Tram has to be stored between 20 and 25^{o}C.

Medicinrådets vurdering af klinisk merværdi for encorafenib i kombination med binimetinib til behandling af ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation

Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at encorafenib i kombination med binimetinib til behandling af patienter med ikke-resektabel eller metastastisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinjebehandling med en BRAF-MEK-hæmmer giver en **ikke-dokumenterbar klinisk merværdi** sammenlignet med dabrafenib i kombination med trametinib. Evidensens kvalitet vurderes at være meget lav.

Medicinrådet vurderer, at encorafenib i kombination med binimetinib til behandling af patienter med ikke-resektabel eller metastastisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med en BRAF-MEK-hæmmer giver **ingen klinisk merværdi** sammenlignet med dabrafenib i kombination med trametinib. Evidensens kvalitet vurderes at være meget lav.

Handelsnavn	Braftovi i kombination med Mektovi
Generisk navn	Encorafenib i kombination med binimetinib
Firma	Pierre Fabre
ATC-kode	L01XE46 L01XE41
Virkningsmekanisme	Encorafenib: BRAF-hæmmer Binimetinib: MEK 1/2 hæmmer
Administration/dosis	Encorafenib 450 mg 1 gang dagligt, oral tablet behandling. Binimetinib 45 mg 2 gange dagligt, oral tablet behandling
EMA-indikation	Encorafenib i kombination med binimetinib til behandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	30. januar 2019 8. februar 2019 41497 1.1
Fagudvalgets sammensætning og sekretariatets arbejdsgruppe	Se afsnit 12

Definition af klinisk merværdi:

Medicinrådet kategoriserer lægemidlets kliniske merværdi i en af følgende kategorier:

Kategori 1. Stor merværdi: Vedvarende og stor forbedring i effektforhold der ikke tidligere er opnået med et relevant behandlingsalternativ. Eksempler herpå er sygdomsremission, markant stigning i overlevelsestid, langvarigt fravær af alvorlige sygdomssymptomer eller udtalt fravær af alvorlige bivirkninger.

Kategori 2. Vigtig merværdi: Markant forbedring, eksempelvis lindring af sygdomstilstand, moderat stigning i overlevelsestid, lindring af alvorlige symptomer, fravær af alvorlige bivirkninger og væsentligt fravær af andre bivirkninger.

Kategori 3. Lille merværdi: Moderat forbedring, f.eks. reduktion i ikkealvorlige sygdomssymptomer eller fravær af bivirkninger.

Kategori 4. Ingen merværdi: Ingen merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 5. Negativ merværdi: Negativ merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 6. Ikkedokumenterbar merværdi: Ikkedokumenterbar merværdi sammenlignet med standardbehandling/ andre behandlinger. Effektforskellen kan ikke kvantificeres ud fra det videnskabelige datagrundlag.

Om Medicinrådet:

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Forkortelser

AE:	*Adverse Events (uønskede hændelser)*
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens *(Grading of Recommendations Assessment, Development and Evaluation)*
HR:	*Hazard Ratio*
LDH:	Lactatdehydrogenase
LVD:	*Left ventricular dysfunction*
MAP	Mitogen Aktiveret Protein
MAPK:	Mitogen Aktiveret Protein Kinase
OR:	*Odds Ratio*
ORR	*Overall Response Rate*
OS	*Overall Survival*
PFS:	*Progression Free Survival*
RPED:	Retina pigment epitel dystrofi
RR:	Relativ Risiko
QOL:	*Quality of Life*
UNL:	*Upper Normal Limit*

Indhold

1 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af encorafenib i kombination med binimetinib som mulig standardbehandling til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparatorer).

Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om encorafenib i kombination med binimetinib anbefales som mulig standardbehandling.

2 Baggrund

Modermærkekræft opstår i melanocytter i modermærker og er den 4. hyppigste kræftform hos kvinder og den 5. hyppigste hos mænd i Danmark. Ifølge Dansk Modermærkekræft Gruppes (DMG) årsrapport blev der i 2016 registreret 2.778 nye tilfælde i Danmark. Sygdommen optræder hovedsageligt hos personer i aldersgruppen 40 til 70 år, men helt unge rammes også [1].

Stadieinddeling

Stadieinddeling af modermærkekræft baseres på TNM-klassifikationen: Tumor, Node (lymfeknude) og Metastase. Disse parametre siger noget om hvor fremskreden primær tumor er, i form af tykkelsen af tumor, status for spredning (metastaser) til nærmeste lymfeknuderegion (N0 for ingen spredning, N3 for alvorlig spredning) og status for fjernmetastaser (M0 for ingen fjernmetastaser og M1c for alvorlige spredning til indre organer) [2,3].

Prognose

Prognosen for modermærkekræft er generelt god, da de fleste tilfælde opdages tidligt [3,4]. Overlevelsen forventes at stige de kommende år på grund af nye behandlingsmuligheder. Prognosen er bedre, hvis der kun er spredning til huden eller til lymfeknuder fjernt fra tumorstedet (M1a), sammenlignet med spredning til indre organer (M1b, M1c eller M1d).

Nuværende behandling

Den primære behandling af lokaliseret sygdom er operation. Trods operation vil nogle patienter udvikle ikke-resektabel lokalavanceret eller metastatisk modermærkekræft og derfor være kandidater til medicinsk behandling. Fagudvalget estimerer, at der er ca. 330 nye patienter pr. år. De organer, sygdommen hyppigst metastaserer til, er lymfeknuder, lunger, lever og hjerne, men også metastaser til knogler, knoglemarv, milt og andre organer, samt muskler og bindevæv ses. Forekomst af organmetastaser er generelt ensbetydende med en meget dårlig prognose [4]. For stadie IV patienter var der, baseret på danske upublicerede tal, en femårsoverlevelse (OS) på cirka 13 % for alle diagnosticerede med ikke-resektabel melanom i 2012 [5].

Omkring 50 % af disse patienter har en BRAF V600-mutation. BRAF-genet koder for B-Raf proteinet, som er en serin/threonin protein kinase, der aktiverer mitogen aktiveret protein kinase (MAPK) signalvejen. Mutationen er forbundet med øget celledeling og dermed tumorvækst. Mutationsundersøgelsen foretages rutinemæssigt hos patienter med metastaser (regionale eller fjernmetastaser) [4]. Behandlingen med en BRAF kinasehæmmer kombineres med en selektiv hæmmer af MEK1/2, der aktiverer mitogen aktiveret protein (MAP). Kombinationen med en MEK 1/2 hæmmer har resulteret i en forbedret anti-tumor aktivitet og forebygger udvikling af resistens mod BRAFV600 hæmmer behandling.

Der er godkendt både immunterapi (PD1-hæmmere og et CTLA4-antistof, herefter kaldet checkpoint-hæmmere) og proteinkinasehæmmere (BRAF- og MEK1/2-hæmmere) til behandling af patienter med ikke-resektabel eller metastatisk modermærkekræft. I Danmark er standardbehandlingen checkpointhæmmere, uanset om patienten har en BRAF V600 mutation eller ej. Man foretrækker checkpointhæmmere, fordi der er dokumenteret langtidseffekt på overlevelse, som ikke ses ved de øvrige lægemidler. Dette valg er også afspejlet i den opdaterede vejledning fra Society for Immunotherapy of Cancer version 2.0 publiceret i 2018 [6].

Den godkendte kombination af en BRAF-kinasehæmmere og en MEK1/2 hæmmer (dabrafenib/trametinib) bliver derfor primært anvendt i anden linje [7].

Kombinationsbehandling med en BRAF/MEK hæmmer anvendes dog både i Danmark og internationalt i første linje til patienter med BRAF-mutation, hvis de ikke kan behandles med checkpointhæmmere. Det drejer sig om patienter med følgende karakteristika:

- symptomatiske hjernemetastaser
- laktat-dehydrogenase LDH > ULN*2 (øvre normal grænse)
- stor tumorbyrde
- hurtigvoksende sygdom
- symptomatisk sygdom
  eller
- relative kontraindikationer til immunterapi (f.eks. behandlingskrævende autoimmun sygdom)

Patienter, der behandles med BRAF-MEK1/2 hæmmer i anden linje efter checkpointhæmmere har ikke samme karakteristika som kandidater til førstelinjebehandling.

Omkring 50 – 60 patienter bliver årligt behandlet med kombinationen i første linje og 55-60 patienter i anden linje.

Anvendelse af det nye lægemiddel

Encorafenib er en selektiv hæmmer af BRAF kinasen og binimetinib er en selektiv hæmmer af MEK1/2. Dosis er 450 mg encorafenib én gang dagligt og 45 mg binimetinib to gange dagligt.

Encorafenib i kombination med binimetinib er indiceret til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation.

Behandlingen fortsættes til progression af sygdommen, død eller ophør grundet bivirkninger.

3 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøgningen er valideret af Medicinrådet.

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol som blev godkendt i Medicinrådet 11. september 2018. Protokollen er udarbejdet af fagudvalget vedrørende modermærkekræft efter Medicinrådets gældende metoder. Ansøgers endelige ansøgning blev godkendt den 13. november 2018.

4 Litteratursøgning

Ansøgers litteratursøgninger opfylder Medicinrådets præspecificerede kriterier. Ansøger har jf. protokollen foretaget en systematisk søgning efter kliniske studier, der tillader en sammenligning af encorafenib i kombination med binimetinib (herefter encorafenib/binimetinib) og drabafenib i kombination med trametinib (herefter dabrafenib/trametinib). Ansøger har foretaget én søgning for effekt og sikkerhed og én for livskvalitet.

Ansøger har identificeret publikationer fra to randomiserede ublindede kliniske studier (RCT), COLUMBUS [8,9] og COMBI-V [10], som ligger til grund for ansøgers indirekte sammenligning.

I de to studier sammenlignes behandling med encorafenib/binimetinib og drabafenib/trametinib med en fælles komparator, vemurafenib. Den indirekte sammenlignende analyse mellem de to studier kan således bidrage til at besvare de kliniske spørgsmål i protokollen. I tillæg til de to hovedstudier er der identificeret to publikationer fra COLUMBUS studiet med data med længere opfølgningstid på samlet overlevelse og uønskede hændelser [11,12] og livskvalitet [13]. Der er også identificeret én publikation fra COMBI-V studiet med data med længere opfølgningstid på samlet overlevelse [14] og livskvalitet [15–18]. Ansøger refererer også til produktresumeer [19,20] og EPAR for henholdsvis encorafenib og binimetinib [21,22].

Encorafenib/binimetinib:

COLUMBUS studiet:
Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Dummer, R. et al. Lancet Oncol. 2018 [8].

Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCORAFENIB) plus binimetinib (BINIMETINIB) vs vemurafenib (VEM) or encorafenib in BRAF-mutant melanoma. Dummer, R. et al. J. Lancet Oncology 2018 [9].

Adverse events of special interest in the phase 3 COLUMBUS study. Gogas, H. et al. J. Clin. Oncol. 2018 [12].

Quality-of-Life (QoL) in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCORAFENIB) Plus Binimetinib (BINIMETINIB) Versus Vemurafenib (VEM) or ENCORAFENIB in BRAF-Mutant Melanoma. Gogas, H et al. Ann. Oncol. Sep. 2017 [13].

Dabrafenib/trametinib:

COMBI-V studie:
Improved overall survival in melanoma with combined dabrafenib and trametinib. Robert, C. et al. N. Engl. J. Med. 2015 [10].

Three-year estimate of overall survival in COMBI-V, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. Robert, C. et al. Ann.Oncol. 2016 [14].

Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-V): results of a phase 3, open-label, randomised trial. Grob, J. J et al. Lancet Oncol. 2015. [23].

COMBI-V: Health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with BRAF V600 metastatic melanoma (MM). Grob, J. J et al. Eur. J. Cancer. 2015. [24]

Analysis of patient-reported outcomes by disease progression status in patients (pts) with BRAF V600-mutant metastatic melanoma in the COMBI-d and COMBI-V trials. Robert, C et al. Ann. Oncol. Conf. 41st Eur. Soc. Med. Oncol. Congr. ESMO. 2016. [15] Abstract med en pooled analyse af COMBI-V og COMBI-D.

Health-related quality-of-life (HRQOL) impact of dabrafenib (D) and trametinib (T) vs BRAF inhibitor (BRAFi) monotherapy by lactate dehydrogenase (LDH) in patients (pts) with BRAF V600-mutant melanoma. Grob, J. J et al. Ann. Oncol. Conf. 41st Eur. Soc. Med. Oncol. Congr. ESMO, 2016 [17]. Abstract med en pooled analyse af COMBI-V og COMBI-D.

Abstracts for COLUMBUS og COMBI-V studierne er fundet og medsendt, men bliver ikke anvendt i den kliniske vurdering.

Fra evidens til kategori. Medicinrådet vurderer den kliniske merværdi af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som "kritiske", "vigtige" og "mindre vigtige". I vurderingen af klinisk merværdi vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Den kliniske merværdi kategoriseres først enkeltvis pr. effektmål, hvorefter der foretages en vurdering af den samlede kategori for lægemidlet på tværs af effektmålene. Kategoriseringen pr. effektmål foretages på baggrund af absolutte og relative værdier for det enkelte effektmål. Den relative effekt beskrives med et estimat og et konfidensinterval, der sammenholdes med generiske væsentlighedskriterier. Den absolutte effekt sammenholdes med den i protokollen beskrevne "mindste klinisk relevante forskel". Den endelige kategorisering af lægemidlets kliniske merværdi er en delvis kvalitativ proces, hvor der foretages en vurdering af det samlede datagrundlag på tværs af effektmålene.

Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk merværdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

5 Databehandling

Klinisk spørgsmål 1

Til besvarelse af klinisk spørgsmål 1, hvor encorafenib/binimetinib sammenlignes med dabrafenib/trametinib til patienter, der er kandidater til førstelinjebehandling med en BRAF/MEK hæmmer, har ansøger ikke indsendt data på patienter med de specifikke patientkarakteristika (jf. afsnit 2): symptomatiske hjernemetastaser, laktat-dehydrogenase LDH > ULN*2 (øvre normal grænse), stor tumorbyrde, hurtigvoksende sygdom, symptomatisk sygdom eller relative kontraindikationer til immunterapi (f.eks. behandlingskrævende autoimmun sygdom) men derimod på en bredere patientpopulation.

Vurdering af datagrundlag

Medicinrådets sekretariat og fagudvalget finder, at vurderingen af klinisk spørgsmål 1 ikke kan basere sig på de indsendte analyser med følgende bemærkninger:

- De patienter i studierne, der fik BRAF/MEK hæmmer i første linje, havde ikke de patientkarakteristika, som blev defineret i protokollen jvf. afsnit 2. Forskellen mellem de ønskede og de fremsendte data er for store til, at fagudvalget kan udtale sig om den kliniske merværdi af behandlingen i første linje.

Klinisk spørgsmål 2
Til besvarelse af klinisk spørgsmål 2, hvor encorafenib/binimetinib sammenlignes med dabrafenib/trametinib til patienter, der er kandidater til andenlinjebehandling med en BRAF/MEK hæmmer, har ansøger udført en indirekte sammenlignende analyse og anvendt Buchers metode. Analysen indeholder data fra COLUMBUS (encorafenib/binimetinib) og COMBI-V (dabrafenib/trametinib) studierne. Hverken COLUMBUS- eller COMBI-V belyser behandling i andenlinje efter checkpoint-hæmmer behandling.

Vurdering af datagrundlag
Medicinrådets sekretariat og fagudvalget finder, at vurderingen af klinisk spørgsmål 2 kan basere sig på de indsendte analyser med følgende bemærkninger:

- Langt de fleste patienter i COLUMBUS og COMBI-V studierne modtog interventionen (en BRAF/MEK hæmmer) som førstelinjebehandling. Det afviger fra dansk klinisk praksis og det kliniske spørgsmål, hvor patienterne skulle have modtaget en checkpointhæmmer som førstelinje-behandling. I studierne er der et begrænset antal patienter, der har modtaget checkpointhæmmere som førstelinjebehandling. Specifikt var der kun 4 % (6 patienter) i COLUMBUS studiet, der havde modtaget en checkpointhæmmer i førstelinje og ingen patienter i COMBI-V studiet. Fagudvalget mener dog, at de kan anvende de indsendte analyser til at sammenligne interventionerne som andenlinjebehandling, da studierne er sammenlignelige hvad angår patientkarakteristika. Det, at patienterne afviger fra populationen defineret i det kliniske spørgsmål, mindsker dog tiltroen til evidensen, hvilket afspejles i GRADE vurderingen
- Ansøger har indsendt fortrolige kvalitative data på livskvalitet, og effektmålet kan derfor ikke vurderes. Sammenligning bliver derfor foretaget narrativt med tilgængelige data fra EPAR.
- Ansøger har indsendt data for uønskede hændelser (adverse events (AE)) og ikke for bivirkninger (uønskede hændelser relateret til behandling: adverse reactions (AR)), som specificeret i protokollen. Bivirkningsprofilerne vil blive belyst i en kvalitativ gennemgang.
- De relative effektforskelle på effektmålet duration of response (DoR) bliver ikke anvendt, da varighed af respons ikke er defineret for hele patientpopulationen i de to studier. Data er kun for de patienter, der oplever respons.
- Begge inkluderede studier af intervention og komparator er ublindede, og der er derfor risiko for bias. COLUMBUS studiets effektmål er vurderet ved en blindet uafhængig review komité (BIRC), hvorimod effektmålene i COMBI-v studiet er investigatorbedømt. Dette fremhæves i vurderingen af evidensens kvalitet.
- Ansøger har ikke belyst effektmålet overall respons rate (ORR) ved hjernemetastaser pga. et meget lille patientantal i denne subgruppe i COLUMBUS studiet med encorafenib/binimetinib. Hjernemetastaser var et eksklusionskriterie i COMBI-V studiet. Datagrundlaget for en indirekte sammenlignende analyse er derfor ikke til stede.

Indirekte sammenligninger
- Den indirekte sammenlignende analyse tager udgangspunkt i de relative værdier fra primær-studierne.
- I den indirekte sammenligning er den relative forskel mellem encorafenib/binimetinib og dabrafenib/ trametinib estimeret ved brug af Buchers metode. Den estimerede relative forskel bruges til at

estimere den absolutte forskel ved at beregne hændelsesraten i encorafenib/binimetinib gruppen ud fra hændelsesraten i dabrafenib/trametinib gruppen (f.eks. hvis relativ forskel mellem encorafenib/binimetinib og dabrafenib/trametinib = 0,9 og hændelsesraten i dabrafenib/trametinib er 30 %, så er hændelsesraten i encorafenib/binimetinib gruppen 30 x 0,9 = 27 og den absolutte risikoreduktion (ARR) = 30 - 27 = 3 procentpoint).

- Ansøger har indsendt data på uønskede hændelser og ORR som odds ratio (OR). Medicinrådets sekretariat har omregnet OR til relativ risiko (RR) (se bilag 2).
- Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Tidshorisont

- Den ønskede tidshorisont blev defineret som længst mulig opfølgningstid med ønske om en median overlevelse eller en 1 års OS-rate. Den mediane opfølgningstid i COLUMBUS studiet var 36,8 måneder for encorafenib/binimetinibarmen og > 36 måneder i COMBI-v studiet for dabrafenib/ trametinibarmen.

6 Klinisk merværdi

6.1 Konklusion klinisk spørgsmål 1

Klinisk spørgsmål1: Hvilken klinisk merværdi tilbyder encorafenib i kombination med binimetinib sammenlignet med dabrafenib i kombination med trametinib til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinjebehandling med en BRAFMEK hæmmer

Jf. afsnit 5 var forskellen mellem de ønskede og de fremsendte data for stor til, at fagudvalget kan lave en reel vurdering af den kliniske merværdi i en relevant population som defineret i dansk klinisk praksis i første linje jvf. afsnit 2.

Fagudvalget finder derfor, at encorafenib/binimetinib til patienter med ikke-resektabel eller metastastisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinjebehandling med en BRAF-MEK hæmmer giver en **ikke-dokumenterbar klinisk merværdi**.

6.2 Konklusion klinisk spørgsmål 2

Hvilken klinisk merværdi tilbyder encorafenib i kombination med binimetinib sammenlignet med dabrafenib i kombination med trametinib til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med en BRAF/MEK hæmmer?

Jf. afsnit 5 vil fagudvalget foretage en vurdering af encorafenib/binimetinib sammenlignet med dabrafenib/ trametinib, som anvendes i dansk klinisk praksis i anden linje.

Fagudvalget vurderer, at encorafenib/binimetinib til patienter med ikke-resektabel eller metastastisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med en BRAF-MEK hæmmer giver **ingen klinisk merværdi** (meget lav evidenskvalitet).

6.2.1 Gennemgang af studier

COLUMBUS (encorafenib/binimetinib versus vemurafenib) [8,9]:

Karakteristika
Studiet er et todelt randomiseret ublindet fase III studie (effekt og sikkerhed). Der ses i denne vurdering kun på den første del, som sammenligner behandling med kombinationen af encorafenib 450 mg én gang dagligt og binimetinib 45 mg to gange dagligt med vemurafenib 960 mg to gange dagligt. Udover dette var der en tredje arm, der ikke belyses i denne indirekte sammenligning, der sammenligner encorafenib i kombination med binimetinib med encorafenib 300 mg alene. I alt blev 577 patienter med metastatisk modermærkekræft med BRAF V600-mutation randomiseret 1:1:1 til behandling med encorafenib/binimetinib, behandling med vemurafenib eller behandling med encorafenib 300 mg alene. Studiets inklusionsperiode var 30. december 2013 til 10. april 2015.

Studiet er et multicenterstudie, som inkluderede patienter fra 162 hospitaler i 28 lande. Patienterne blev inkluderet i studiet, hvis de var ≥ 18 år og opfyldte inklusionskriterierne; lokal avanceret (AJCC stadie IIIB, IIIC eller IV), ikke-resektabel eller metastatisk modermærkekræft eller ukendt primær modermærkekræft (tilføjelse), havde BRAF V600E eller BRAF V600K mutation, havde ECOG performancestatus 0 eller 1, var behandlingsnaive eller havde haft progression på eller efter tidligere førstelinjebehandling med immunterapi for resektabel lokalavanceret eller metastatisk melanom. Tidligere adjuverende behandling var tilladt (f.eks. IFN, IL-2, anden immunterapi end IFN og IL-2, strålebehandling eller kemoterapi). Patienter måtte ikke tidligere været behandlet med en BRAF- eller MEK-hæmmer, tidligere været i behandling med systemisk kemoterapi (tilføjelse 2014), radioterapi eller andre forsøgslægemider end immunterapi.

Patienterne blev stratificeret på baggrund af sygdomsstadium (AJCC IIIB, IIIC, IVM1a, IVM1b eller IVM1c), performancestatus 0 eller 1 samt BRAF-mutationsstatus (BRAF V600E eller BRAF V600K). Efter en tilføjelse til protokollen i 2013, blev BRAF-mutationsstatus erstattet med tidligere behandling med førstelinje immunterapi (ja eller nej) som stratificeringsfaktor.

Studiets primære endepunkt var progressionsfri overlevelse (PFS), der defineres som tiden fra randomisering til første dokumenterede sygdomsprogression eller død uanset årsag. Studiets sekundære endepunkt var samlet overlevelse (OS), overall respons rate (ORR), tid til respons (TTR), sygdomskontrol rate (DCR), varighed af respons (DOR), sikkerhed og tolerans, performancestatus (PS), livskvalitet vurderet ved EORTC QLQC30, EQ-5D og FACT-M. Endepunkterne blev vurderet ved en blindet uafhængig central reviewkomite (BIRC), mens lokal investigatorvurdering blev anvendt til støttende analyser.

Median opfølgningstid var ved det seneste data cut-off (november 2017) 36,8 måneder.
Sikkerhedsanalyserne er gennemført ved en cut-off i november 2016. Alle effektanalyser er udført på intention to treat-populationen (ITT). Sikkerhedsanalyser blev udført på alle patienter, som havde modtaget behandling med mindst en dosis af studiemedicin, og som havde mindst en post-baseline sikkerhedsvurdering (safety populationen). Relevante baselinekarakteristika ses i tabel 1.

COMBI-V (dabrafenib/trametinib versus vemurafenib) [10]:
Studiet er et randomiseret ublindet fase III studie. Det er et multicenterstudie med patientinklusion fra 193 centre på verdensplan. I alt blev 704 patienter med metastatisk modermærkekræft med BRAF V600-mutation randomiseret 1:1 til behandling med dabrafenib 150 mg to gange dagligt i kombination med trametinib 2 mg én gang dagligt eller behandling med vemurafenib 960 mg to gange dagligt. Studiets inklusionsperiode var fra juni 2012 til oktober 2013.

Inklusionskriterierne var målbar sygdom ifølge RECIST (version 1.1,15) og en performancestatus (ECOG) på 0 eller 1. Patienter, som havde været i behandling for hjernemetastaser med ingen stigning i læsions-størrelse i mindst 12 uger, kunne også inkluderes. Patienterne blev ekskluderet, hvis de tidligere havde fået

systemisk anti-cancerbehandling for avanceret eller metastatisk modermærkekræft. Tidligere adjuverende behandling med immunterapi, herunder ipilimumab, var tilladt, hvis denne var afsluttet ≥ 8 uger inden inklusion. Tidligere kirurgisk behandling af hjernemetastaser samt adjuverende helhjerne strålebehandling var tilladt.

Patienterne blev stratificeret ud fra BRAF-mutationsstatus (BRAF V600E/V600K) og laktatdehydrogenase niveau (LDH).

Det primære endepunkt var OS, der defineres som tid fra randomisering til død uanset årsag. De sekundære endepunkter var PFS, ORR, DOR og sikkerhed. Det var ikke muligt at skifte fra vemurafenibarmen til kombinationsarmen før den uafhængige monitoreringskomite anbefalede at stoppe studiet, pga. signaler om høj effekt i kombinationsgruppen. Efter den anbefaling blev protokollen i stedet udvidet, så det blev tilladt for patienter i vemurafenibarmen at skifte til kombinationsarmen. Endepunkterne blev vurderet af investigator ud fra Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Sikkerhed blev vurderet i klinikken.

Ved data cut-off (februar 2016) var der opfølgningstid på > 3 år. Alle effektanalyser er udført på intention to treat-populationen (ITT). Sikkerhedsanalyser blev udført på alle patienter, som havde modtaget behandling med mindst en dosis af studiemedicin, og som havde mindst en post-baseline sikkerhedsvurdering (safety populationen). Relevante baselinekarakteristika ses i tabel 1.

Fagudvalget er opmærksom på, at der er forskel i kalendertidspunktet for de to studiers inklusionsperiode (COLUMBUS og COMBI-V). De tilgængelige muligheder for behandling ved progression har ændret sig over en kort periode med ipilimumab, der blev tilgængelige i flere lande i 2012 og pembrolizumab, der blev tilgængelig fra 2014 gennem EAP (Extensible Authentication Protocol) og senere med en EMA godkendelse i 2015. Dette kan muligvis have en indflydelse på en eventuel cross-over effekt på overlevelse. COLUMBUS studiet inkluderede patienter i perioden fra december 2013 – april 2015 og COMBI-V studiet inkluderede patienter i perioden juni 2012 – oktober 2013.

COMBI-MB (dabrafenib/trametinib) i patientpopulation med hjernemetastaser [26].
Studiet er et multikohorte ikke-blindet fase 2 studie, der evaluerede dabrafenib 150 mg 2 gange daglig og trametinib 2 mg en gang daglig i fire patientkohorter med modermærkekræft og hjernemetastaser. Det er et multicenterstudie med patientinklusion fra 32 centre i Europa, Nordamerika og Australien. Det primære effektmål var respons på hjernemetastaser. Studiets inklusionsperiode var fra februar 2014 til august 2016 med en median opfølgningstid på 6,5 måneder. Studiet inddrages af fagudvalget til belysning af dabrafenib/trametinibs effekt på hjernemetastaser.

Tabel 1: Baseline karakteristika for interventionsarmen i COLUMBUS og COMBI-V [8,10]

	Encorafenib 450 mg i kombination med binimetinib 45 mg (n = 192) COLUMBUS	**Dabrafenib i kombination med trametinib (n = 352) COMBI-v**
Median alder (år)	57,0 (20-89)	55 (18-91)
Køn, mænd – no. (%)	115 (60 %)	208 (59 %)
LDH koncentration ≥ øverste normalgrænse < øverste normalgrænse	 55 (29 %) 137 (71 %)	 118 (34 %) 233 (66 %)
Antal organer involveret – no. (%) 1 2 <3 ≥3	 47 (24 %) 58 (30 %) 87 (45 %)	 177 (50 %) 174 (50 %)
BRAF status - no. (%) V600E V600K	 170 (89 %) 22 (11 %)	 312 (90 %) 34 (10 %)
Tumorstadie – no. (%) IIIb/IIIc IVM1a IVM1b IIIc, IVM1a eller IVM1b IVM1c	 9 (5 %) 26 (14 %) 34 (18 %) 123 (64 %)	 130 (37 %) 221 (63 %)
Tidligere immunterapi – no. (%) Uspecificeret Ipilimumab adjuverende avanceret/metastatisk PD1/PD-L1-hæmmer avanceret/metastatisk Interferoner eller interleukiner adjuverende** neoadjuverende avanceret/metastatisk***	 57 (30 %) 2 (1 %) 5 (3 %) 1 (1 %) 51 (27 %) 47 (24 %) 0 4 (2 %)	 61 (17 %)*
Performance status (ECOG) – no. (%) 0 1	 136 (71 %) 56 (29 %)	 248 (71 %) 102 (29 %)

*inkluderede adjuverende behandling med: interferoner, interleukin-2, granulocyte-makrofag stimulerende faktor, gangliosider, imiquimod, ipilimumab og forsøgs anti-neplastisk vaccine

**interferon alfa og beta

***interferon alfa og interleukin 2

Population

Fagudvalget finder, at baselinekarakteristika mellem de to studier er sammenlignelige. Imidlertid afviger patientpopulationen i begge studier fra den relevante danske patientpopulation, som typisk er patienter der progredierer efter behandling med en checkpoint-hæmmer i første linje og hvor performancestatus således er væsentligt dårligere.

6.2.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som hhv. kritiske og vigtige, følger nedenfor. Den samlede kliniske merværdi af encorafenib/binimetinib sammenlignet med dabrafenib/trametinib baseres på længst mulig opfølgningstid.

Overall survival (OS) (kritisk)
Overlevelse defineres som tiden fra behandlingsstart til død, uafhængig af årsag. OS ønskes opgjort som median OS eller OS-rate ved 1 år. Opfølgningstiden for de tilgængelige OS-data for encorafenib/binimetinib er 36,8 måneder og der er 36 måneders data for dabrafenib/trametinib.

Tabel 2. Vurdering af klinisk merværdi: OS

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	Median OS: 3 måneder Ved 1 år: 10 %-point		8,4 måneder [NA; NA]
Relative forskelle	Stor merværdi		
	Vigtig merværdi		
	Lille merværdi		
	Ingen merværdi	Øvre konfidensgrænse >1,0	HR = 0,90 [0,65;1,24]
	Negativ merværdi		
Evidensens kvalitet	Meget lav evidenskvalitet		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Median OS i COLUMBUS studiet var 33,6 måneder for encorafenib/binimetinib sammenlignet med 16,9 måneder for vemurafenib, som giver en absolut effektforskel på 16,7 måneder til fordel for encorafenib/ binimetinib. Median OS i COMBI-v studiet var 26,1 måneder for dabrafenib/trametinib sammenlignet med 17,8 måneder for vemurafenib, som giver en absolut effektforskel på 8,3 måneder til fordel for dabrafenib/ trametinib. Den estimerede absolutte effektforskel mellem studierne på 8,4 måneder til fordel for encorafenib/binimetinib overstiger den mindste klinisk relevante forskel på 3 måneder. Den relative forskel indikerer derimod, at encorafenib/binimetinib har ingen klinisk merværdi sammenlignet med dabrafenib/trametinib vedrørende OS, idet den øvre konfidensgrænse er > 1,0.

Fagudvalget vurderer samlet, at encorafenib/binimetinib har en **ingen klinisk merværdi** sammenlignet med dabrafenib/trametinib for effektmålet median OS (meget lav evidenskvalitet).

Bivirkninger (kritisk)
Ansøger har indsendt bivirkningsdata for encorafenib/binimetinib COLUMBUS og dabrafenib/trametinib fra COMBI-V i form af uønskede hændelser (adverse events (AE)), som dækker over både de protokol-definerede bivirkninger (adverse reactions (AR)) og øvrige hændelser opstået under behandlingen. Fagudvalget vurderer, at bivirkninger kan belyses ved uønskede hændelser, men det påvirker fagudvalgets tiltro til effektestimatet og graderes ned i GRADE gennemgangen.

Udover en kvalitativ vurdering af uønskede hændelser relateret til behandling med encorafenib/binimetinib ønskes uønskede hændelser også opgjort som andel af patienter, der oplever én eller flere uønskede hændelser af grad 3-4, samt andelen af patienter med behandlingsophør som følge af uønskede hændelser. Data opgøres først separat for de to måleenheder, og til sidst foretages en samlet merværdikategorisering baseret på de opgjorte data, samt den kvalitative vurdering af bivirkningsprofilen.

Uønskede hændelser grad 3-4
Dataanalysen er foretaget på safety-populationerne, dvs. inkluderede patienter, der har modtaget mindst én behandlingsdosis.

Effektmålet er opgjort som andelen af patienter, som oplever én eller flere grad 3-4 uønskede hændelser.

Tabel 3. Vurdering af klinisk merværdi: Andel af patienter, som oplever en eller flere uønskede hændelser grad 3-4

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	En forskel på 10 %-point		5 %-point [-7; 17]
Relative forskelle	Stor merværdi		
	Vigtig merværdi		
	Lille merværdi		
	Ingen merværdi	Øvre konfidensgrænse > 1,00	RR = 1,03 [0,78;1,29]
	Negativ merværdi		
Evidensens kvalitet	Meget lav evidenskvalitet		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen.
Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Patienter i behandling med encorafenib/binimetinib i COLUMBUS og dabrafenib/trametinib i COMBI-v oplevede færre grad 3-4 uønskede hændelser sammenlignet med patienter i behandling med vemurafenib (57,8 % vs. 63,4 % og 52,0 % vs. 63,0 %). Den absolutte forskel mellem encorafenib/binimetinib og dabrafenib/trametinib versus vemurafenib er 5,4 %-point til fordel for encorafenib/binimetinib, hvilket ligger under den prædefinerede mindste klinisk relevante forskel.

Den relative effektforskel indikerer, at encorafenib/binimetinib har ingen klinisk merværdi sammenlignet med dabrafenib/trametinib, da konfidensintervallet krydser 1,0.

Samlet vurderer fagudvalget, at behandling med encorafenib/binimetinib har **ingen klinisk merværdi** sammenlignet med dabrafenib/trametinib, hvad angår grad 3-4 uønskede hændelser (meget lav evidenskvalitet).

Behandlingsophør som følge af uønskede hændelser

Tabel 4. Vurdering af klinisk merværdi: Andel af patienter, med behandlingsophør som følge af uønskede hændelser

	Forhåndsdefineret grundlag for vurdering		Medicinrådets vurdering
Absolutte forskelle	En forskel på 5 %-point		-5 %-point [-13; 3]
Relative forskelle	Stor merværdi		
	Vigtig merværdi		
	Lille merværdi		
	Ingen merværdi	Øvre konfidensgrænse > 1,00	RR: 0,70 [0,36;1,30]
	Negativ merværdi		
Evidensens kvalitet	Meget lav evidenskvalitet		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen.
Anden kolonne indeholder data fra ansøgning, som indgår i Medicinrådets vurdering.

Færre patienter i behandling med encorafenib/binimetinib end vemurafenib oplevede i COLUMBUS-studiet behandlingsophør (12,5 % vs. 16,7 %). I COMBI-v studiet oplevede flere patienter i dabrafenib/trametinib-armen end vemurafenibarmen behandlingsophør pga. uønskede hændelser (13,0 % vs. 12,0 %). Den absolutte forskel mellem encorafenib/binimetinib og dabrafenib/trametinib versus vemurafenib er 5 %-point til fordel for encorafenib/binimetinib, hvilket ligger over den prædefinerede mindste klinisk relevante forskel. Fagudvalget bemærker, at frekvensen af behandlingsophør grundet uønskede hændelser er ens i de to

interventions-arme, mens forskellen ses i vemurafenib komparatorarmene.

Den relative forskel indikerer, at encorafenib/binimetinib har ingen klinisk merværdi sammenlignet med dabrafenib/trametinib, da konfidensintervallet krydser 1,0.

Samlet vurderer fagudvalget, at behandling med encorafenib/binimetinib **ingen klinisk merværdi** har sammenlignet med dabrafenib/trametinib, hvad angår behandlingsophør som følge af uønskede hændelser (meget lav evidenskvalitet).

Kendte bivirkninger
Som supplement til de to ovenstående kvantitative vurderinger foretager fagudvalget en kvalitativ gennemgang af de uønskede hændelser relateret til behandling med encorafenib/binimetinib. Gennemgangen baseres på sikkerhedsdata fra tre studier (COLUMBUS (del 1), LOGIC-2 og studie CMEK162X2110 [21,22], som også ligger til grund for EMA-godkendelsen. Derudover inddrages produktresumeerne for encorafenib og binimetinib for en detaljeret beskrivelse af bivirkningerne [19,20].

I den kvalitative gennemgang fokuserer fagudvalget på bivirkninger med særligt fokus på pyrexi (feber), fototoxicitet og hjertets pumpefunktion (LVD) samt dosisreduktion og interaktion med stråleterapi, jf. protokollen. Herudover har fagudvalget valgt også at fokusere på hypertension, leverpåvirkning og gastrointestinale bivirkninger (kvalme, opkast og diarre). Den kvalitative gennemgang vil blive holdt op overfor behandling med dabrafenib/trametinib, se tabel 5 [27].

Tabel 5. Oversigt over udvalgte bivirkninger og uønskede hændelser

	Encorafenib/binimetinib Behandlingsrelaterede uønskede hændelser		**Dabrafenib/trametinib** Behandlingsrelaterede uønskede hændelser	**Dabrafenib/trametinib** Uønskede hændelser
	Alle grader	**Grad 3-4**	**Alle grader**	**Grad 3-4**
Pyrexi	17,2 %	2,9 %	47 %	4 %
Fototoxicitet	4 %	0,4 %	3 %	0 %
Påvirkning af hjertets pumpefunktion	8,4 %	1,1 %	8 %¤	4 %
Hypertension	11,7 %	5,5 %	13 %	< 1 %
Kvalme	41,6 %	2,6 %	23 %	< 1 %
Opkast	28,1 %	2,2 %	17 %	1 %
Diarre	38 %	3,3 %	20 %	1 %
Påvirkning af leverfunktion#	15,7 %	5,5 %	10 %	4 %

Forhøjet ASAT/ALAT, ¤ Er kun opgjort som "uønskede hændelser"

Ved den kvalitative gennemgang af bivirkninger forbundet med de to kombinationer af en BRAF hæmmer og en MEK1/2 hæmmer fremhæver fagudvalget at:

- Fagudvalget bemærker, at pyrexi grad 1-2 kan være en stor gene for patienter, der tager lægemidlerne over en længere periode. Derfor vægter fagudvalget frekvensen af alle grader af bivirkninger med pyrexi, hvor der ses en stor forskel i frekvensen for encorafenib/binimetinib sammenlignet med dabrafenib/trametinib (17,2 % vs. 47%).
- Påvirkning af hjertets pumpefunktion er en kendt bivirkning ved behandling med dabrafenib/ trametinib med en frekvens grad 3-4 (kun opgjort som uønsket hændelse) på 4 % versus 1,1 % for encorafenib/binimetinib. Fagudvalget fremhæver, at de er opmærksomme på denne risiko, hvor der bør være indskærpet opmærksomhed på patienternes følgesygdomme (komorbiditet).

- Behandling med encorafenib/binimetinib er forbundet med hyppigere forekomst af forhøjet blodtryk grad 3-4 og fagudvalget er opmærksomme på denne risiko.
- Behandling med encorafenib/binimetinib er forbundet med hyppigere forekomst af kvalme, opkast og diarré sammenlignet med dabrafenib/trametinib, inklusiv svære tilfælde (grad 3-4). Fagudvalget vægter igen frekvensen af alle grader af bivirkninger med gastrointestinale gener, da lægemidlet tages over en længere periode og kan være en belastning for patienterne. Det kan ikke udelukkes, at forekomsten af gastrointestinale gener vil give anledning til flere kontrolbesøg, pausering af behandling, dosisjusteringer og muligvis behandlingsophør.
- Begge kombinationer af en BRAF hæmmer og en MEK1/2 hæmmer er forbundet med fototoxicitet og påvirkning af leverfunktions blodprøver. Begge er håndterbare i klinisk praksis.

Fototoxicitet førte til dosisreduktion hos 0,4 % af patienterne. LVD førte til behandlingsophør hos 0,4 % og behandlingspause eller dosisreduktion i 6,6 % af patienterne. LVD var generelt reversibelt efter behandlings-pause eller dosisreduktion.

På baggrund af den kvalitative gennemgang vurderer fagudvalget, at bivirkningsprofilerne mellem lægemidlerne adskiller sig væsentligt i forhold til feber, kardiovaskulære og gastrointestinale bivirkninger, hvilket bør inddrages i den konkrete kliniske situation.

Samlet konklusion, bivirkninger
I vurderingen har fagudvalget bemærket, at bivirkningsprofilerne mellem lægemidlerne er forskellige. På baggrund af bivirkningsprofilerne kan fagudvalget dog ikke sige, om det ene lægemiddel er at foretrække frem for et andet.

Fagudvalget vurderer, at de uønskede hændelser generelt er håndterbare og reversible. På baggrund af dette vurderer fagudvalget, at samlet for effektmålet bivirkninger har encorafenib/binimetinib **ingen klinisk merværdi** sammenlignet med dabrafenib/trametinib (meget lav evidenskvalitet), tabel 5.

Tabel 6. Samlet vurdering af effektmålet bivirkninger

Effektmål	**Vigtighed**	**Merværdi**	**Evidenskvalitet**
Uønskede hændelser grad 3-4 (AE's)	Kritisk	Ingen	Meget lav
Behandlingsophør som følge af uønskede hændelser (AE's)	Kritisk	Ingen	Meget lav
Samlet vurdering		**Ingen**	**Meget lav**

Progression free survival (PFS) (vigtig)
PFS defineres som tiden fra studierandomisering til første dokumentation af progression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 eller dødsfald. PFS ønskes opgjort som median PFS. Opfølgningstiden for de tilgængelige PFS-data for encorafenib/binimetinib er 36,8 måneder og der er 36 måneders data for dabrafenib/trametinib.

Tabel 7. Vurdering af klinisk merværdi: PFS

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	Median PFS: 3 måneder		3,5 måneder [NA;NA]
Relative forskelle	Stor merværdi		
	Vigtig merværdi		
	Lille merværdi		
	Ingen merværdi	Øvre konfidensgrænse >1,0	HR = 0,77 [0,56;1,06]
	Negativ merværdi		
Evidensens kvalitet	Meget lav		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Median PFS i COLUMBUS studiet var 14,9 måneder for encorafenib/binimetinib sammenlignet med 7,3 måneder for vemurafenib. Median PFS i COMBI-V studiet var 11,4 måneder for dabrafenib/trametinib sammenlignet med 7,3 måneder for vemurafenib. Den estimerede absolutte effektforskel på 3,5 måneder til fordel for encorafenib/binimetinib overstiger netop den mindste klinisk relevante forskel på 3 måneder. Den relative forskel indikerer, at encorafenib/binimetinib har ingen klinisk merværdi sammenlignet med dabrafenib/trametinib vedrørende PFS, idet den øvre konfidensgrænse er > 1,0.

Fagudvalget vurderer samlet, at encorafenib/binimetinib har en **ingen klinisk merværdi** sammenlignet med dabrafenib/trametinib for effektmålet median PFS (meget lav evidenskvalitet).

Livskvalitet (vigtig)
Livskvalitetsdata for encorafenib/binimetinib er endnu upublicerede, hvorfor data fra EPAR'en er anvendt til en narrativ gennemgang. Livskvalitet belyses ud fra effektmålene FACT-M, EORTC-QLQ-C30 og EQ-5D-5L [22]. Medianen blev ikke nået for effektmålet FACT-M (klinisk relevant ændring: 10%) i encorafenib/ binimetinib armen, men for vemurafenib armen blev medianen nået ved 22,1 måneder, med en HR på 0,46 (95 % CI: 0,29;0,72) mellem de to arme. Forværring i EORTC-QLQ-C30 (klinisk relevant ændring: 10 %) blev observeret 7 måneder senere for encorafenib/binimetinib armen sammenlignet med vemurafenib (23,9 måneder vs. 16,6 måneder). Der var ingen forskel i effektmålet EQ-5D-5L mellem encorafenib/binimetinib og vemurafenib.

COMBI-V studiet belyser livskvalitet primært med EQ-5D (klinisk relevant ændring: > 0,08 i index score). Der blev set klinisk relevant ændring fra baseline for dabrafenib/trametinib sammenlignet med vemurafenib på EQ-5D score ved uge 16, uge 48 og ved sygdomsprogression.

På baggrund af den narrative gennemgang, hvor begge studier (COLUMBUS og COMBI-V) viser en favorabel effekt sammenholdt med den fælles komparator vemurafenib, vurderer fagudvalget, at encorafenib/binimetinib har **ingen klinisk merværdi** sammenlignet med dabrafenib/trametinib for effektmålet livskvalitet (meget lav evidenskvalitet).

Overall response rate (ORR) (vigtig)
ORR defineres som andelen af patienter, som opnår delvist eller komplet respons. ORR ønskes opgjort som andelen af patienter, der oplever respons. Opfølgningstiden for de tilgængelige ORR-data for encorafenib/ binimetinib er 36,8 måneder og der er 36 måneders data for dabrafenib/trametinib.

Tabel 8. Vurdering af klinisk merværdi: ORR

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	Andel af patienter, der opnår respons: 10 %-point		9,0 %-point [-3,0;21,0]
Relative forskelle	Stor merværdi		
	Vigtig merværdi		
	Lille merværdi	Nedre konfidensgrænse >1,0	RR = 1,17 [1,01;1,28]
	Ingen merværdi		
	Negativ merværdi		
Evidensens kvalitet	Meget lav		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen.
Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

ORR for encorafenib/binimetinib vs. vemurafenib var hhv. 63,5 % og 40,8 % og for dabrafenib/trametinib vs. vemurafenib hhv. 67 % og 53 %. Den estimerede absolutte effektforskel på 9,0 %-point til fordel for encorafenib/binimetinib ligger under den mindste klinisk relevante forskel på 10 %-point. Den relative forskel indikerer, at encorafenib/binimetinib har en lille klinisk merværdi sammenlignet med dabrafenib/ trametinib vedrørende ORR, idet den nedre konfidensgrænse er > 1,0. Fagudvalget bemærker, at forskellen ligger i vemurafenib armen, hvilket kan skyldes forskellen mellem studierne ved vurdering af effektmål med en hhv. uafhængig review komité i COLUMBUS studiet og investigatorvurdering i COMBI-V studiet.

Fagudvalget vurderer samlet, at encorafenib/binimetinib har en **ingen klinisk merværdi** sammenlignet med dabrafenib/trametinib for effektmålet median ORR (meget lav evidenskvalitet).

Duration of response (DoR)(vigtig)
DoR defineres som tiden fra første dokumenterede respons (bekræftet komplet respons eller delvis respons) til datoen for progression eller død som følge af modermærkekræft. DoR ønskes opgjort som median DoR. Opfølgningstiden for de tilgængelige DoR-data for encorafenib/binimetinib er 36,8 måneder og der er 36 måneders data for dabrafenib/trametinib.

Tabel 9. Vurdering af klinisk merværdi: DoR

	Forhåndsdefineret grundlag for vurdering		Resultater
Absolutte forskelle	Median DoR: 2 måneder		0,1 måned [NA;NA]
Relative forskelle	Stor merværdi		
	Vigtig merværdi		
	Lille merværdi		
	Ingen merværdi		
	Negativ merværdi		
Evidensens kvalitet	Meget lav		

Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen.
Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

Median DoR i COLUMBUS studiet var 18,6 måneder for encorafenib/binimetinib sammenlignet med 12,3 måneder for vemurafenib. Median DoR i COMBI-V studiet var 13,8 måneder for dabrafenib/trametinib sammenlignet med 7,6 måneder for vemurafenib. Den estimerede absolutte effektforskel på 0,1 måned til fordel for encorafenib/binimetinib overstiger ikke den mindste klinisk relevante forskel på 2 måneder. Jf. afsnit 5 bliver de relative effektforskelle ikke anvendt.

Fagudvalget vurderer samlet, at encorafenib/binimetinib har en **ingen klinisk merværdi** sammenlignet med dabrafenib/trametinib for effektmålet median DoR (meget lav evidenskvalitet).

Overall response rate (ORR) - hjernemetastaser (vigtig)
Jf. afsnit 5 har ansøger ikke belyst effektmålet overall respons rate ved hjernemetastaser.

Fagudvalget finder derfor, at encorafenib/binimetinib til patienter med ikke-resektabel eller metastastisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med en BRAF-MEK hæmmer giver en **ikke-dokumenterbar klinisk merværdi** for effektmålet ORR ved hjernemetastaser med meget lav evidenskvalitet.

6.2.3 Evidensens kvalitet

Evidensens kvalitet for behandling med encorafenib/binimetinib sammenlignet med dabrafenib/trametinib til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med en BRAF-MEK hæmmer, er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 3.

Der er udarbejdet én GRADE-profil for klinisk spørgsmål 2. Evidensens kvalitet er nedgraderet for inkonsistens og indirectness (der foreligger ét studie for hhv. encorafenib/binimetinib og dabrafenib/ trametinib), da der er tale om en indirekte sammenligning, manglende datagrundlag på den ønskede population samt bivirkninger, som belyses indirekte ved at være opgjort som uønskede hændelser.

6.2.4 Konklusion for klinisk spørgsmål 2

Fagudvalget vurderer, at encorafenib/binimetinib giver en **ingen klinisk merværdi** for patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinje-behandling med en BRAF-MEK hæmmer sammenlignet med dabrafenib/trametinib med en meget lav evidenskvalitet.

Tabel 9. Samlet oversigt over vurdering af effektmål

Effektmål	**Vigtighed**	**Merværdi**	**Evidenskvalitet**
Overall Survival (OS)	Kritisk	Ingen	Meget lav
Bivirkninger: - AEs grad 3-4 - Behandlingsophør grundet AEs	Kritisk	Ingen	Meget lav
Progression free survival (PFS)	Vigtig	Ingen	Meget lav
Livskvalitet	Vigtig	Ingen	Meget lav
Overall responsrate (ORR)	Vigtig	Ingen	Meget lav
Duration of response (DoR)	Vigtig	Ingen	Meget lav
Overall responsrate (ORR) hjernemetastaser	Vigtig	Ikke-dokumenterbar	Meget lav
Samlet vurdering		**Ingen**	**Meget lav**

- Fagudvalget vurderer, med udgangspunkt i en indirekte sammenlignende analyse, at encorafenib/ binimetinib mindst har samme effekt som dabrafenib/trametinib.

- Fagudvalget bemærker, at bivirkningsprofilen er forskellig mellem lægemidlerne. Fagudvalget kan med udgangspunkt i datagrundlaget ikke sige, om det ene lægemiddel er at foretrække frem for et andet.
- Der foreligger kliniske data, der understøtter behandling af patienter med hjernemetastaser med dabrafenib/trametinib [26]. Dette anvendes i dansk klinisk praksis til patienter med symptomatiske hjernemetastaser.

7 Andre overvejelser

Fagudvalget ønsker at belyse specifikke forhold ved indtag af medicinen:

- Indtag af lægemidlerne: dabrafenib/trametinib indtages mindst en time før et måltid eller to timer efter, hvorimod encorafenib/binimetinib kan indtages uafhængigt af fødeindtag.
- Antal af tabletter: Fulddosis encorafenib/binimetinib medfører indtag af 6+6 tabletter dagligt og dabrafenib/trametinib betyder indtag af 4+1 tabletter dagligt.

Begge forhold kan risikere at påvirke patientens compliance og dermed behandlingens effekt.

8 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at encorafenib i kombination med binimetinib til patienter med ikke-resektabel eller metastastisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinjebehandling med en BRAF-MEK hæmmer giver en **ikke-dokumenterbar klinisk merværdi** sammenlignet med dabrafenib i kombination med trametinib (meget lav evidenskvalitet).

Fagudvalget vurderer, at encorafenib/binimetinib til patienter med ikke-resektabel eller metastastisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med en BRAF-MEK hæmmer giver en **ingen klinisk merværdi** sammenlignet med dabrafenib i kombination med trametinib (meget lav evidenskvalitet).

9 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at encorafenib i kombination med binimetinib til patienter med ikke-resektabel eller metastastisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinjebehandling med en BRAF-MEK hæmmer giver en **ikke-dokumenterbar klinisk merværdi** sammenlignet med dabrafenib i kombination med trametinib (meget lav evidenskvalitet).

Medicinrådet vurderer, at encorafenib/binimetinib til patienter med ikke-resektabel eller metastastisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med en BRAF-MEK hæmmer giver en **ingen klinisk merværdi** sammenlignet med dabrafenib i kombination med trametinib (meget lav evidenskvalitet).

10 Relation til eksisterende behandlingsvejledning

Medicinrådet har besluttet at udarbejde en fælles regional behandlingsvejledning for terapiområdet. Indtil da

vurderer fagudvalget, at encorafenib/binimetinib kan anses som ligestillet med dabrafenib/trametinib som første- og andenlinjebehandling til patienter uden hjernemetastaser på baggrund af effekt og bivirkninger.

11 Referencer

1. Danish Melanoma Group. Dansk Melanom Database. National Årsrapport 2016 [internet]. Annual report. 2016. Tilgængelig fra: https://www.sundhed.dk/sundhedsfaglig/kvalitet/kliniske-kvalitetsdatabaser/kraeft/dansk-melanom-database/

2. American Cancer Society. Melanoma of the Skin Staging. 2009.

3. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long G V, Ross MI, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin [internet]. 2017 [citeret 9. maj 2018];67(6):472–92. Tilgængelig fra: http://doi.wiley.com/10.3322/caac.21409

4. Rådet for Anvendelse af Dyr Sygehusmedicin (RADS). RADS Baggrundsnotat for metastaserende malignt melanom. 2016.

5. Dansk Melanom Gruppe. Danish Metastatic Melanoma Database. 2017.

6. Sullivan RJ, Atkins MB, Kirkwood JM, Agarwala SS, Clark JI, Ernstoff MS, et al. An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: Version 2.0. J Immunother Cancer. 2018;6(1):1–23.

7. Rådet for Anvendelse af Dyr Sygehusmedicin (RADS). RADS Behandlingsvejledning for metastaserende malignt melanom. København; 2016.

8. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol [internet]. 2018 [citeret 25. juni 2018];19(5):603–15. Tilgængelig fra: http://linkinghub.elsevier.com/retrieve/pii/S1470204518301426

9. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol [internet]. 2018;19(5):603–15. Tilgængelig fra: http://dx.doi.org/10.1016/S1470-2045(18)30497-2

10. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib, supplemtary. N Engl J Med [internet]. 2015;372(1):30–9. Tilgængelig fra: http://www.nejm.org/doi/10.1056/NEJMoa1412690

11. Dummer R et al. Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF -mutant melanoma. Reinhard. J Clin Oncol. 2018;45(3):131–6.

12. Gogas H, Dummer R, Ascierto PA, Arance A, Mandalà M, Liszkay G. Adverse events of special interest in the phase 3 COLUMBUS study. J Clin Oncol. 2018;36(15_suppl):9567–9567.

13. Gogas H, Dummer R, Ascierto PA, Arance A, Mandala M, Liszkay G, et al. Quality-of-life (QoL) in COLUMBUS part 1: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in braf-mutant melanoma. Ann Oncol [internet]. 2017;28(suppl_5). Tilgængelig fra: http://academic.oup.com/annonc/article/doi/10.1093/annonc/mdx377.031/4109318/1245PQualityoflife-QoL-in-COLUMBUS-part-1-A-phase

14. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroyakovskiy D, et al. Three-year estimate of overall survival in COMBI-v, a randomized, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) with vemurafenib (Vem) as first-line therapy in

patients (pts) with unresectable or metastatic BRA. Ann ofOncology [internet]. 2016;27(Supplement 6):vi552-vi587. Tilgængelig fra: http://linkinghub.elsevier.com/retrieve/pii/S0959804916318202

15. Robert C, Schadendorf D, Long G V., Stroyakovskiy D, Levchenko E, Chiarion-Sileni V, et al. Analysis of patient-reported outcomes by disease progression status in patients (pts) with BRAF V600-mutant metastatic melanoma in the COMBI-d and COMBI-v trials. Ann Oncol Conf 41st Eur Soc Med Oncol Congr ESMO. 2016;27(no pagination).

16. Grob JJ, Amonkar MM, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-l. Lancet Oncol. 2015;16(13):1389–98.

17. Grob JJ, Robert C, Long G V., Stroyakovskiy D, Levchenko E, Chiarion-Sileni V, et al. Health-related quality-of-life (HRQOL) impact of dabrafenib (D) and trametinib (T) vs BRAF inhibitor (BRAFi) monotherapy by lactate dehydrogenase (LDH) in patients (pts) with BRAF V600-mutant melanoma. Ann Oncol Conf 41st Eur Soc Med Oncol Congr ESMO. 2016;27(no pagination).

18. Grob JJ, Amonkar M, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. COMBI-v: Health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with BRAF V600 metastatic melanoma (MM). Eur J Cancer [internet]. 2015;51(Supplement 3):S682–3. Tilgængelig fra: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L72068548

19. European Medicines Agency EMA. Mektovi - SUMMARY OF PRODUCT CHARACTERISTICS. 2018.

20. European Medicines Agency EMA. Braftovi - Summary of Product characteristics. London: European Medicines Agency; 2018.

21. European Medicines Agency EMA. Assessment report Mektovi. 2018;

22. European Medicines Agency EMA. Assessment report Braftovi. 2018;

23. Grob JJ, Amonkar MM, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-l. Lancet Oncol [internet]. 2015;16(13):1389–98. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/26433819

24. Grob JJ, Amonkar M, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. COMBI-v: Health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with BRAF V600 metastatic melanoma (MM). Eur J Cancer. 2015;51:S682–3.

25. Gruppe DM. Melanoma.dk\guidelines. 2018.

26. Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017;18(7):863–73.

27. European Medicines Agency EMA. Assessment report - Mekinist (Trametinib), Tafinlar (Dabrafenib). 2015;44(September). Tilgængelig fra: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002604/WC500196276.pdf

12 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende modermærkekræft
Forvaltningslovens §4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
Marco Donia Klinisk lektor, afdelingslæge, ph.d.	Lægevidenskabelige Selskaber og Region Hovedstaden
Medlemmer	**Udpeget af**
Adam Andrzej Luczak Overlæge	Region Nordjylland
Trine Heide Øllegaard Afdelingslæge, ph.d.	Region Midtjylland
Lars Bastholt Overlæge	Region Syddanmark
Kan ikke udpege	Region Sjælland
Jakob Henriksen 1. reservelæge	Dansk Selskab for Klinisk Farmakologi (DSKF)
Ingen udpegning	Dansk Selskab for Sygehusapoteksledelse (DSS)
Mathilde Skaarup Larsen Overlæge, ph.d.	Dansk Patologiselskab (DPAS)
Lisbet Rosenkrantz Hölmich Klinisk forskningslektor, overlæge, dr.med.	Dansk Selskab for Plastik- og Rekonstruktionskirurgi (DSPR) og Dansk Melanom Gruppe (DMG)
Søren Chrestensen Patient/patientrepræsentant	Danske Patienter
Lene Ottesen Patient/patientrepræsentant	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Jette Østergaard Rathe (projekt- og metodeansvarlig) Charlotte Wulf Johansen (koordinator) Pernille Koefoed Arrevad (sundhedsvidenskabelig konsulent) Tenna Bekker (teamleder) Bettina Fabricius Christensen (informationsspecialist) Jan Odgaard-Jensen (statistiker)

13 Ændringslog

Version	Dato	Ændring
1.1	08.02.2019	Vedr. Medicinrådets konklusion side 1: Medicinrådets vurdering af førstelinjebehandling fremgik ikke af konklusionen, hvorfor dette er nu tilpasset i konklusionen samt konsekventrettet i afsnit 8 og 9. Konklusionen var tidligere: *Medicinrådet vurderer, at encorafenib i kombination med binimetinib til behandling af ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation giver* ***ingen klinisk merværdi*** *sammenlignet med dabrafenib i kombination med trametinib. Evidensens kvalitet vurderes at være meget lav.* Vedr. afsnit 8 og 9: Den kliniske merværdi i begge konklusioner var ikke sat overfor komparator. Disse er nu tilpasset ved indsættelse af sætning "*sammenlignet med dabrafenib i kombination med trametinib*". Vedr. afsnit 10: Medicinrådets sekretariat er blevet opmærksomme på, at i relationen til eksisterende behandlingsvejledning fremgik det ikke tydeligt, at det gælder for både første- og andenlinjebehandling, hvorfor dette nu er indsat. Afsnit 10 var tidligere: *Medicinrådet har besluttet at udarbejde en fælles regional behandlingsvejledning for terapiområdet. Indtil da vurderer fagudvalget, at encorafenib/binimetinib kan anses som ligestillet med dabrafenib/trametinib til patienter uden hjernemetastaser på baggrund af effekt og bivirkninger.* Vedr. afsnit 2 "nuværende behandling" Ansøger henviser i deres høringssvar til ESMO guidelines, hvor både immunterapi og BRAF-MEK hæmmere anbefales som førstelinjebehandling. Fagudvalget har på denne baggrund foretaget en ændring i formuleringen. Afsnit 2 "nuværende behandling" var tidligere: *Dette valg er også afspejlet i opdaterede vejledninger fra internationale selskaber [6].* Vedr. afsnit 6.2.1: I høringssvaret er der gjort opmærksom på, at overall respons rate og objectiv respons rate er blevet anvendt til effektmålet ORR. Dette ensrettes, så ORR konsekvent er overall response rate. Afsnit 6.2.1 var tidligere: *Studiets sekundære endepunkt var samlet overlevelse (OS), objektiv respons rate (ORR), ….* Vedr. afsnit 6.2.2 "overall survival" Ansøger har i høringssvaret oplyst at efterfølgende behandling efter progression er angivet i EPARen. Som følge af høringssvaret har fagudvalget valgt at fjerne en formulering. Afsnit 6.2.2 "overall survival" omfattede tidligere:

		Fagudvalget hæfter sig ved, at der ikke er givet oplysninger om hvilken behandling patienterne i studiet har fået efter progression, og at en mulig cross-over effekt derfor ikke kan udelukkes. Der er forskel i kalender-tidspunktet for de to studier og dermed mulighederne for effektiv tilgængelig behandling.
1.0	30.01.2019	Godkendt af Medicinrådet

14 Bilag 1: Tabel med omregning af OR over til RR

	Effektmål	OR	OR lower	OR upper	ACR	RR	RR lower	RR upper	Absolut effekt (95% CI)
Kliniske spørgsmål 1	Grad 3-4 uønskede hændelser	1,07	0,64	1,80	50,0 %	1,03	0,78	1,29	**0,05 (-0,07; 0,17)**
	Behandlingsophør som følge af uønskede hændelser	0,67	0,33	1,36	12,0 %	0,70	0,36	1,30	**-0,05 (-,013; 0,03)**
	ORR	1,77	1,04	3,02	67,0 %	1,17	1,01	1,28	**0,09 (-0,03; 0,21)**

ACR - antaget hændelsesrate i komparatorgruppen (baseret på combi-v og combi-d studierne)
RR = OR/(1-ACR*(1-OR))
RRlower = ORlower/(1-ACR*(1-ORlower))
RRupper = ORupper/(1-ACR*(1-ORupper))

15 Bilag 2: GRADE-evidensprofiler

15.1 Cochrane Risk of Bias

Risk of bias – COLUMBUS	Vurdering	Begrundelse
Random sequence generation (selection bias)	• Lav risiko for bias	Stratificeret randomisering. Stratificeret efter sygdomsstadie (IIIB,IIIC, IVM1b eller IVM1c), ECOG performance status 0-1 og BRAF mutationsstatus (V600E eller V600K). protokolændring december 2013 erstattede tidligere førstelinje immunterapi BRAF mutationsstatus
Allocation concealment (selection bias)	• Lav risiko for bias	Randomisering med et IVRS (interactive voice response system), hvor patienter blev randomiseret 1:1:1 til en af de tre behandlingsgrupper (encorafenib/binimetinib:vemurafenib:encorafenib monoterapi).
Blinding of participants and personnel (performance bias)	• Høj risiko for bias	Både patienter og personale var ikke-blindede.
Blinding of outcome assessment (detection bias)	• Lav risiko for bias	En uafhængig review komité vurderede effektmål.
Incomplete outcome data (attrition bias)	• Lav risiko for bias	Alle effektmål blev analyseret i "intention-to-treat-population" og på prædefineret subgruppeniveau.
Selective reporting (reporting bias)	• Lav risiko for bias	De effektmål, der beskrives i metodeafsnittet, er rapporteret i studiet.
Other bias		

Risk of bias – COMBI-v	Vurdering	Begrundelse
Random sequence generation (selection bias)	• Lav risiko for bias	Stratificeret randomisering LDH >/≤ øvre normal grænse og BRAF mutationsstatus (V600E eller V600K).
Allocation concealment (selection bias)	• Lav risiko for bias	Randomisering med et IVRS (interactive voice response system), hvor patienter blev randomiseret 1:1 til en af de to behandlings-grupper (dabrafenib/trametinib:vemurafenib).
Blinding of participants and personnel (performance bias)	• Høj risiko for bias	Både patienter og personale var ikke-blindede.
Blinding of outcome assessment (detection bias)	• Høj risiko for bias	Investigator-vurderet effektmål.
Incomplete outcome data (attrition bias)	• Lav risiko for bias	Alle effektmål blev analyseret i "intention-to-treat-population" og på prædefineret subgruppeniveau.
Selective reporting (reporting bias)	• Lav risiko for bias	De effektmål, der beskrives i metodeafsnittet, er rapporteret i studiet.
Other bias		

15.2 GRADE-evaluering af evidenskvaliteten til vurdering af den kliniske merværdi af encorafenib/binimetinib

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**encorafenib_binimetinib**	**dabrafenib_trametinib**	**Relative (95% CI)**	**Absolute (95% CI)**		
overall survival												
2	randomised trials	serious	serious [a]	serious [b]	not serious	none	105/192 (54.7%)	155/352 (44.0%)	**HR 0.90** (0.65 to 1.24)	**8,4 måneder**	⨁◯◯◯ VERY LOW	CRITICAL
uønskede hændelser grad 3-4												
2	randomised trials	serious	serious [a]	very serious [c]	not serious	none	111/192 (57.8%)	182/350 (52.0%)	**HR 1.03** (0.78 to 1.29)	**5 % point (-0,07;0,7)**	⨁◯◯◯ VERY LOW	CRITICAL
behandlingsophør som følge af uønskede hændelser												
2	randomised trials	serious	serious [a]	serious [c]	not serious	none	24/191 (12.6%)	45/350 (12.9%)	**RR 0.70** (0.36 to 1.30)	-5 % point (-0,13;0,03)	⨁◯◯◯ VERY LOW	CRITICAL
Progressionn Free Survival												
2	randomised trials	serious	serious [a]	serious [b]	not serious	none	113/192 (58.9%)	166/352 (47.2%)	**HR 0.77** (0.56 to 1.06)	**3,5 måneder**	⨁◯◯◯ VERY LOW	IMPORTANT
livskvalitet												
2	randomised trials	serious	serious [a]	serious [b]	serious [d]	none	Narrativ syntese				⨁◯◯◯ VERY LOW	IMPORTANT

Fortsættes næste side…

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	encorafenib_binimetinib	dabrafenib_trametinib	Relative (95% CI)	Absolute (95% CI)		
overall respons rate												
2	randomised trials	serious	serious [a]	serious [b]	not serious	none	122/192 (63.5%)	226/352 (64.2%)	**RR 1.17** (1.01 to 1.28)	**9 % point (-3,0;21,0)**	⨁◯◯◯ VERY LOW	IMPORTANT
duration of response												
2	randomised trials	serious	serious [a]	serious [b]	not serious	none	Ikke belyst			0,1 måned	⨁◯◯◯ VERY LOW	IMPORTANT
overall respons rate hjernemetastaser												
2	randomised trials	serious	serious [a]	serious [b]	serious [d]	none	Manglende data				⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

a. Ét studie for encorafenib/binimetinib og ét studie for dabrafenib/trametinib
b. En indirekte sammenligning
c. en indirekte sammenligning og bivirkning belyst som uønskede hændelser fremfor behandlingsrelaterede uønskede hændelser
d. pga. manglende data har en kvantitativ vurdering ikke været mulig

<

Application to the Medicine Council for the assessment of the clinical added value of BRAFTOVI® in combination with MEKTOVI® in unresectable or metastatic melanoma for BRAF-mutated patients

Contains confidential information

Contents

List of Figures

List of Tables

1. Basic information

Table 1: Contact information

Name	Andrew Poll
Title	Head of Market Access UK, Ireland & Nordics
Area of responsibility	Clinical, economic and negotiation
Phone	0044 7825 162982
E-mail	andrew.poll@pierre-fabre.com

Table 2: Overview of the pharmaceutical

Proprietary name	BRAFTOVI®	MEKTOVI®
Generic name	Encorafenib	Binimetinib
Marketing authorisation holder in Denmark	Pierre Fabre Medicament	Pierre Fabre Medicament
ATC code	L01XE46	L01XE41
Pharmacotherapeutic group	Antineoplastic agent, protein kinase inhibitor	Antineoplastic agent, protein kinase inhibitor
Active substance(s)	Encorafenib 50 and 75 mg	Binimetinib 15 mg
Pharmaceutical form(s)	Hard capsules	Film-coated tablets
Mechanism of action	Encorafenib is a potent and highly selective ATP-competitive small molecule B-Raf proto-oncogene (BRAF) inhibitor [1–3] that suppresses the RAF/MEK/ERK pathway in tumour cells expressing mutated forms of BRAF kinase, inhibiting BRAF V600E, D and K mutation-positive melanoma cell growth. A slow dissociation half-life of over 30 hours results in prolonged pERK inhibition.	Binimetinib is an ATP-uncompetitive, reversible mitogen/extracellular signal-regulated kinase (MEK) inhibitor that inhibits proliferation and viability of human BRAF-mutant melanoma cell lines and inhibits tumour growth [4,5].
	In combination, encorafenib and binimetinib concomitantly inhibit the two kinases, RAF and MEK, of the RAF/MEK/ERK pathway, resulting in improved inhibition of intracellular signalling and higher anti-tumour activity.	
Dosage regimen	The recommended dose of encorafenib is 450 mg (six 75 mg capsules) orally once	The recommended dose of binimetinib is 45 mg (three 15 mg tablets) orally twice

	daily when used in combination with binimetinib.	daily approximately 12 hours apart, when used in combination.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	Binimetinib in combination with encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Other approved therapeutic indications	None	None
Will dispensing be restricted to hospitals?	Yes	Yes
Combination therapy and/or co-medication	Combination therapy with binimetinib	Combination therapy with encorafenib
Packaging – types, sizes/number of units, and concentrations	Braftovi 50 mg hard capsules Polyamide/aluminium/PVC/aluminium blister containing 4 capsules. Each pack contains 28 hard capsules. Braftovi 75 mg hard capsules Polyamide/aluminium/PVC/aluminium blister containing 6 capsules. Each pack contains 42 hard capsules [1]	Perforated Alu-PVC/PVDC blister containing 12 tablets. Each pack contains 84 tablets [4]
Orphan drug designation	No	No

Abbreviations: ATP, Adenosine triphosphate; BRAF, B-Raf proto-oncogene; MEK, mitogen/extracellular signal-regulated kinase; PVC, polymerising vinyl chloride; PVDC, poly-vinylidene dichloride

2. Abbreviations

Abbreviation	Definition
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AE(s)	Adverse event(s)
ASCO	American Society of Clinical Oncology
ATP	Adenosine triphosphate
BID	Twice daily
BIRC	Blinded independent review committee
BOR	Best overall response
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRAFi	BRAF inhibitor
CI	Confidence interval
CR	Compete response
CrI	Credible interval
CSR	Clinical study report
Dabra+Tram	Dabrafenib in combination with trametinib
DCFB	Difference in change from baseline
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
Enco+Bini 450	Encorafenib in combination with binimetinib
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	Euroqol-5 dimensions questionnaire
ERK	Extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
FACT-M	Functional Assessment of Cancer Therapy-Melanoma
FAS	Full analysis set
GH	Global Health Status
HR	Hazard ratio
HRQoL	Health-related quality of life
IO	Immuno-oncology
ITC	Indirect treatment comparison
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
MAA	Marketing authorization application
MEK	Mitogen/Extracellular signal-regulated kinase
MEKi	MEK inhibitor
MMRM	Mixed model repeated measures
NE	Not estimable
NICE	National Institute for Health and Care Excellence
NR	Not reported
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazard
PS	Performance status
QD	Once daily
QLQ-C30	Core Quality of Life Questionnaire
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Relative Risk
SD	Stable disease

Abbreviation	Definition
SLR	Systematic literature review
SmPC	Summary of product characteristics
TTR	Time to response

3. Summary

Cutaneous melanoma is the most serious form of skin cancer [6]. Patients are diagnosed mainly at local stage, while only 6.9% have a regional disease (stage III) and 1.1% at metastatic stage (stage IV) [7]. In the Danish national melanoma registry, 2,734 patients with invasive melanoma were recorded in 2017 [7]. Metastatic disease is associated with poor prognosis; 5-year survival rate of 13% for stage IV [8].

In Denmark, 40% to 50% of metastatic patients have melanomas harbouring proto-oncogene B-Raf (BRAF) V600 mutations [9]; there is a substantial unmet need for well-tolerated treatments that delay disease progression and improve survival in these patients. Combination therapies of BRAF inhibitors (BRAFi) with mitogen/extracellular signal-regulated kinase (MEK) inhibitors (MEKi) are treatments of choice for metastatic patients with BRAF-mutant melanoma, giving high response rates and rapid onset of response.

Encorafenib (BRAFTOVI® 50 and 75 mg hard capsules) in combination with binimetinib (MEKTOVI® 15 mg tablets [4,5]; hereafter referred to as Enco+Bini 450), is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (European marketing authorisation: 20th September 2018).

Part 1 of the two-part phase III COLUMBUS trial provides the key evidence on the clinical efficacy, safety and tolerability of Enco+Bini 450 compared with vemurafenib 960 mg twice-daily monotherapy and encorafenib 300 mg once-daily monotherapy, in patients with locally advanced unresectable or metastatic BRAF V600 mutation-positive melanoma [10]. A 46% risk reduction in disease progression or death was observed for patients treated with Enco+Bini 450 versus vemurafenib monotherapy (hazard ratio [HR] 0.54; 95% confidence interval [CI]: 0.41-0.71, p<0.0001) [10]. Median overall survival was 33.6 months (95% CI 24.4-39.2) for patients treated with Enco+Bini 450 versus 16.9 months (95% CI 14.0-24.5) for vemurafenib monotherapy [11]. The progression-free survival in the Enco+Bini 450 arm was 7.6 months longer compared with the vemurafenib arm, with median progression-free survival of 14.9 months (95% CI: 11.0-20.2) and 7.3 months (95% CI: 5.6-7.9), respectively (data cut-off November 2017) [11]. Characteristic toxicities associated with BRAFi/ MEKi combination therapies were generally manageable, reversible, and infrequently associated with treatment discontinuation with Enco+Bini 450, and no serious unexpected adverse events (AEs) of special interest were observed [11].

An indirect treatment comparison was conducted for Enco+Bini 450 versus dabrafenib in combination with trametinib (Dabra+Tram), the comparator of interest for this submission, as per DMC protocol. Numerical benefits in favour of Enco+Bini 450 compared to Dabra+Tram were demonstrated for both overall survival (HR of 0.90 [95% CI: 0.65, 1.24]) and progression-free survival (HR of 0.80 [95% CI: 0.58, 1.11)]). Additionally, in a naïve comparison, the absolute improvement on median overall survival versus vemurafenib was 8.4 months greater for Enco+Bini 450 compared with Dabra+Tram, exceeding the minimum clinically relevant difference of 3 months. For Euroqol-5 dimensions questionnaire (EQ-5D)

index scores, comparability of Enco+Bini 450 and Dabra+Tram was shown through an indirect comparison: difference in pre-progression index score of [redacted] less than the minimal clinically important difference of 0.08 points.

4. Literature Search

A systematic literature review (SLR) was conducted to identify published evidence reporting on the efficacy and safety of available interventions for unresectable or metastatic cutaneous melanoma. A separate SLR was conducted to identify published evidence on the health-related quality of life (HRQoL) of patients with unresectable or metastatic cutaneous melanoma. Both SLRs were conducted in alignment with the method proposed by the Centre for Reviews and Dissemination of the University of York and supported by the National Institute for Health and Clinical Excellence [12]. As the SLRs were conducted within the last 6 months (updated in April 2018), it was deemed that they are an accurate representation of the current state of the literature. Although the protocol outlined by the Medicine Council stipulated the inclusion of brand names, it was expected that all relevant studies would be captured using the generic names alone as clinical trials are usually reported using the generic name of the drug. This was confirmed by conducting literature searches with brand names, over the same time periods as the original and updated clinical SLR; these returned the same number of total records (Appendix A, section A.3, Table A. 3). Therefore, this deviation from the protocol does not affect the results of the SLRs. Although the search criteria were broader than those defined in the protocol, the results were stratified according to therapy class and trial design, which facilitated alignment with the Medicine Council's protocol.

4.1 Databases and search strategy

The scope of the SLRs are defined in terms of the patient population, intervention, comparators, outcomes measures, and study design, i.e. PICOS. Once all criteria had been specified, they were translated into "search strings" after which the search was executed, resulting in the identification of relevant and important evidence. The PICOS statements applied for the clinical (efficacy and safety) and HRQoL searches are presented in Appendix A and Appendix B, respectively.

Searches were conducted using the following databases, using the advanced search of the OVID platform:

- MEDLINE
    - Ovid MEDLINE® Epub Ahead of Print
    - In-Process & Other Non-Indexed Citations
    - Ovid MEDLINE® Daily
    - Ovid MEDLINE and Versions®
- Embase
- The Cochrane Library
    - Central register of controlled trials
    - Database of abstracts of reviews of effects

Searches were limited to English language studies with a date of publication between 01 January 2000 and the date of the search. The searches were conducted using a combination of search terms and keywords for cutaneous melanoma, treatments of interest, and terms related to the study design.

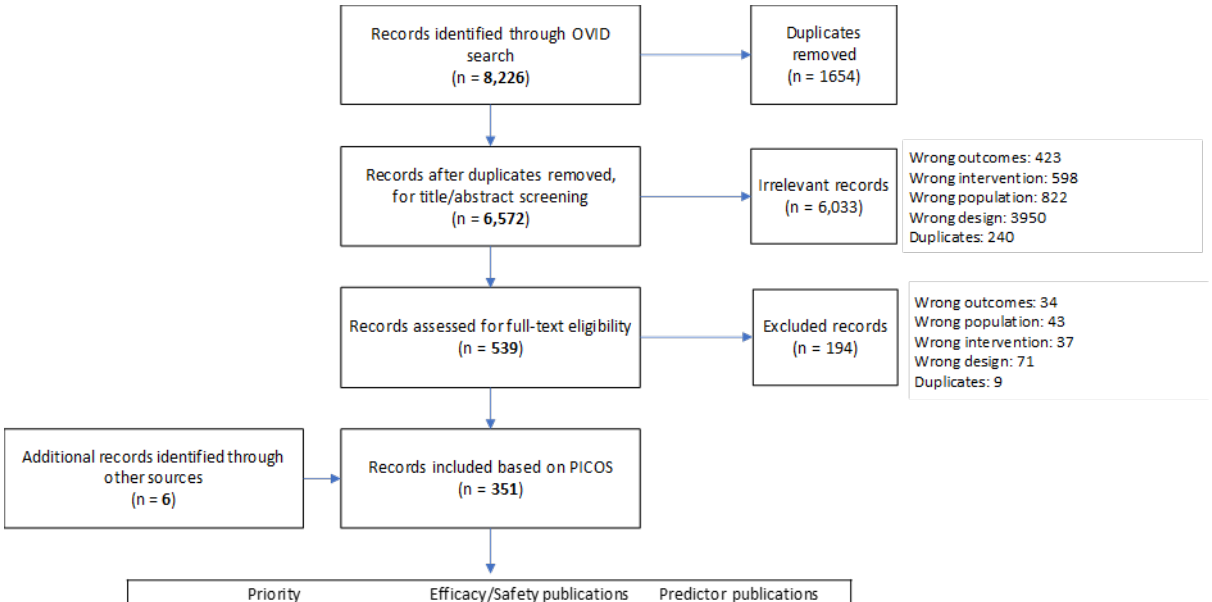
Please refer to Appendix A and Appendix B for full details on the methodologies for the clinical and HRQoL SLR respectively.

4.2 Relevant studies

4.2.1 Systematic literature review: clinical evidence

The clinical search conducted on 14 April 2017 identified a total of 6,572 unique references after removal of duplicate records (Figure 1). Abstract review identified 539 potentially relevant references for full-text review, of which 345 fulfilled the eligibility criteria defined. Supplementary manual searches yielded six additional references (three full-texts and three abstracts) and thus, a total of 351 publications were included.

Figure 1: PRISMA flow diagram for efficacy and safety evidence (searches conducted on 14 April 2017)

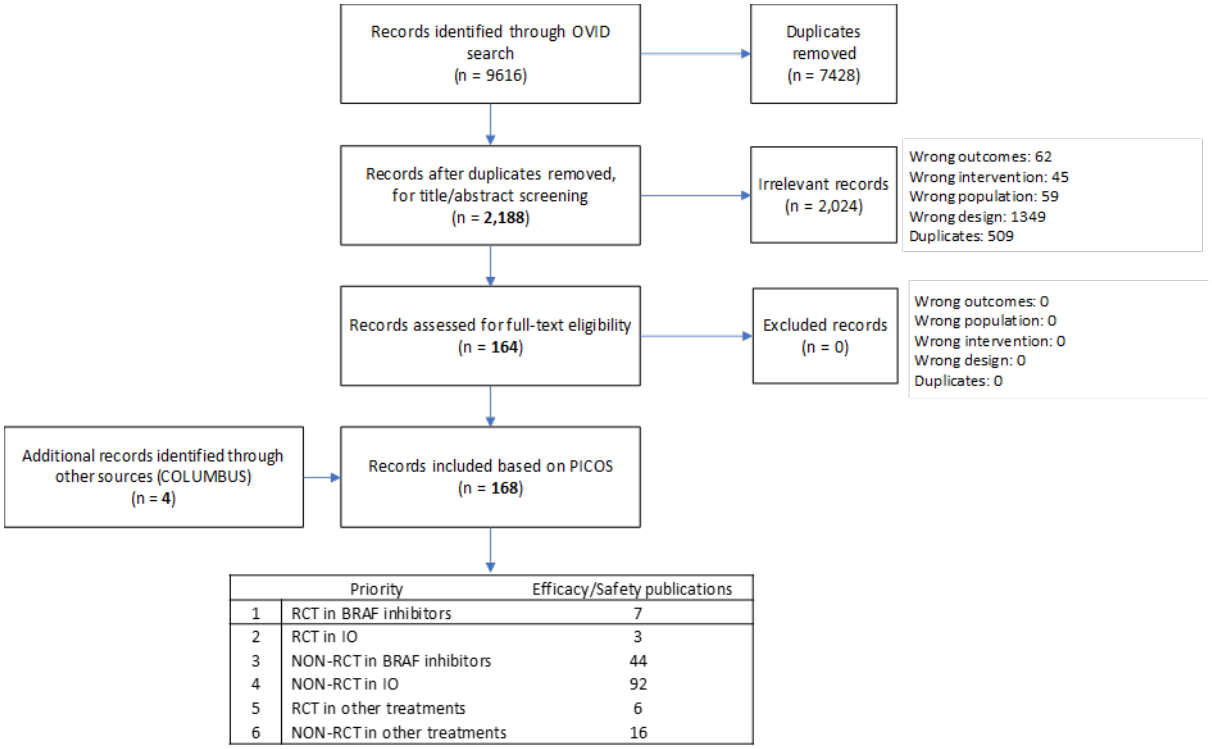


	Priority	Efficacy/Safety publications	Predictor publications
1	RCT in BRAF inhibitors	16	-
2	RCT in IO	8	-
3	NON-RCT in BRAF inhibitors	44	38
4	NON-RCT in IO	64	49
5	RCT in other treatments	21	-
6	NON-RCT in other treatments	76	35

BRAF: B-Raf proto-oncogene, serine/threonine kinase; IO: immuno-oncology; RCT: randomised controlled trial. Note: Efficacy/safety publications include studies that reported protocol defined efficacy and safety outcomes in unresectable and metastatic melanoma patients. Predictor publications included studies that reported correlation of baseline variables to predict the likelihood of melanoma in patients and to facilitate treatment decision in individuals or cohort

The updated clinical search, conducted on 03 April 2018, identified a total of 2,188 additional references after removal of duplicates from the first round of searches conducted in 2017. Abstract review identified 164 potentially relevant references for full-text review, all of which fulfilled the eligibility criteria. In addition, four publications were identified by hand-searching for the COLUMBUS study. Therefore, a total of 168 publications were included, in addition to the original search in 2017, from the updated literature search (Figure 2).

Figure 2: PRISMA flow diagram for efficacy and safety evidence (updated searches on 03 April 2018)



	Priority	Efficacy/Safety publications
1	RCT in BRAF inhibitors	7
2	RCT in IO	3
3	NON-RCT in BRAF inhibitors	44
4	NON-RCT in IO	92
5	RCT in other treatments	6
6	NON-RCT in other treatments	16

BRAF: B-Raf proto-oncogene, serine/threonine kinase; IO: immuno-oncology; RCT: randomised controlled trial. Note: Efficacy/safety publications include studies that reported protocol defined efficacy and safety outcomes in unresectable and metastatic melanoma patients

In Denmark, the only BRAFi/MEKi combination treatment in use is Dabra+Tram [8], which is therefore the comparator of interest for this submission. In total, eight records identified in the clinical SLR reported efficacy and safety data on three relevant RCTs investigating BRAFi, either as monotherapy or in combination with MEKi: COLUMBUS, COMBI-v, COMBI-d (Table 3). Details of publications that were excluded following full text assessment are provided, together with justification for exclusion in a separate excel document entitled “PF_EncoBini_SLR_QoL_Clinical_Excluded_Studies.xlsx”.

Table 3. Relevant clinical studies from the clinical SLR included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
Primary: - Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Dummer, R. et al. *Lancet Oncol.* 2018 [10] **Secondary:** - Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma. Dummer, R. et al. *J. Clin. Oncol.* 2018 [11] - Adverse events of special interest in the phase 3 COLUMBUS study. Gogas, H. et al. *J. Clin. Oncol.* 2018 [13]	**COLUMBUS**	NCT01909453	December 2013 – November 2017	1,2
Primary: - Improved overall survival in melanoma with combined dabrafenib and trametinib. N. Engl. Robert, C. et a. *J. Med.* 2015 [14] **Secondary**: - Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. Robert, C. et al. Ann.Oncol. 2016 [15]	**COMBI-v**	NCT01597908	June 2012 –July 2014	1,2
Primary: - Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. Long. G.V. et al. *N. Engl. J. Med.* 2014 [16] **Secondary:** - Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and	**COMBI-d**	NCT01584648	May 2012 –February 2016	1,2

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
safety analysis of a phase 3 study. Long, G.V et al. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* 2017 [17] - Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. G.V. Long. *The Lancet.* 2015 [18]				

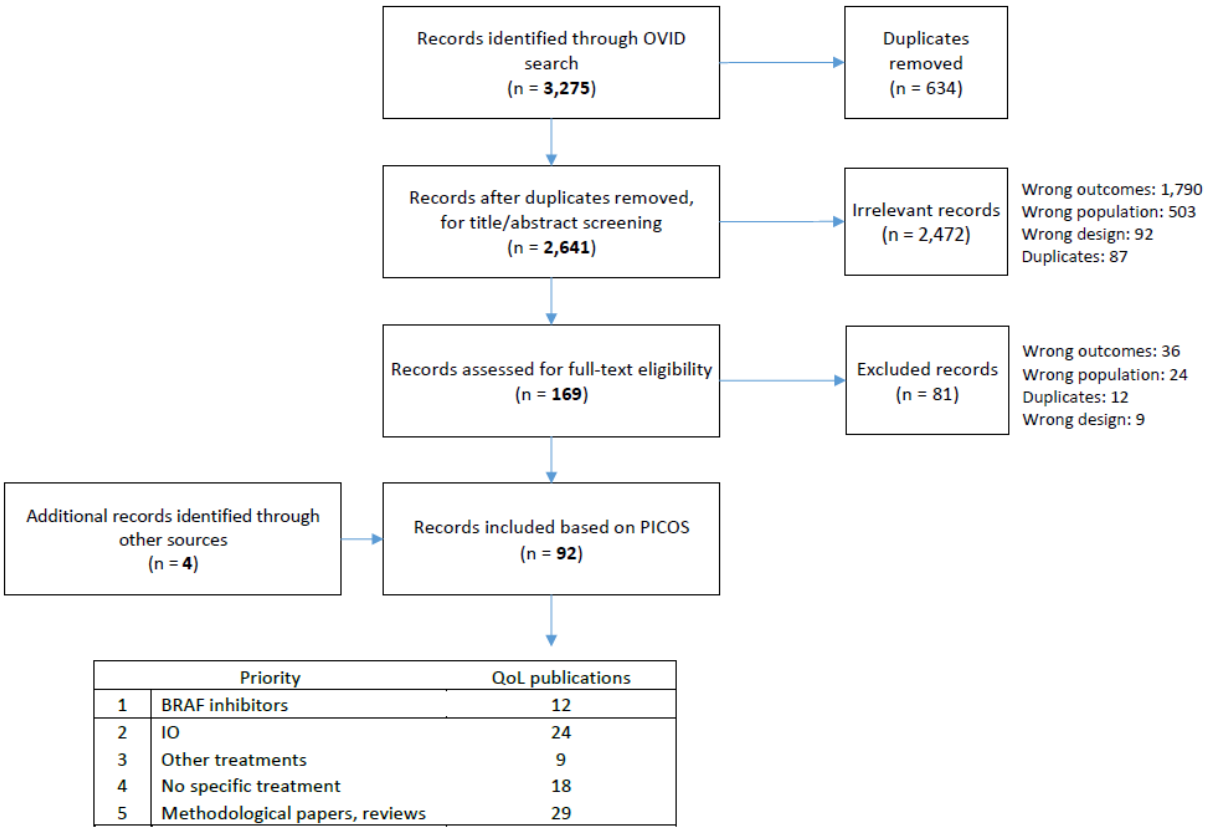
4.2.2 Systematic literature review: health-related quality of life evidence

The HRQoL search conducted in May 2017 identified a total of, 3,275 publications. Following removal of duplicates, 2,641 unique references were retained for title and abstract review. Abstract review identified 169 potentially relevant references for full-text review, of which 88 fulfilled eligibility criteria (see Appendix B). Supplementary manual searches through other sources yielded 4 additional full-text references; thus, a total of 92 studies were included in the review.

The updated clinical searches in April 2018 identified a total of 480 additional references after initial removal of duplicates from the first round of search. Abstract review identified 24 potentially relevant references for full-text review, of which 14 met the eligibility criteria.

The PRISMA flow charts below provide details of the selection process for HRQoL studies. Of the included studies, 16 reported HRQoL results from BRAFi/MEKi RCTs and 27 reported results from immuno-oncology treatment RCTs. Remaining studies were related to other melanoma treatments (n=9), non-treatment specific studies (n=18) or methodological papers/reviews (n=29). Details of publications that were excluded following full text assessment are provided, together with justification for exclusion in a separate excel document entitled “PF_EncoBini_SLR_QoL_Clinical_Excluded_Studies.xlsx”.

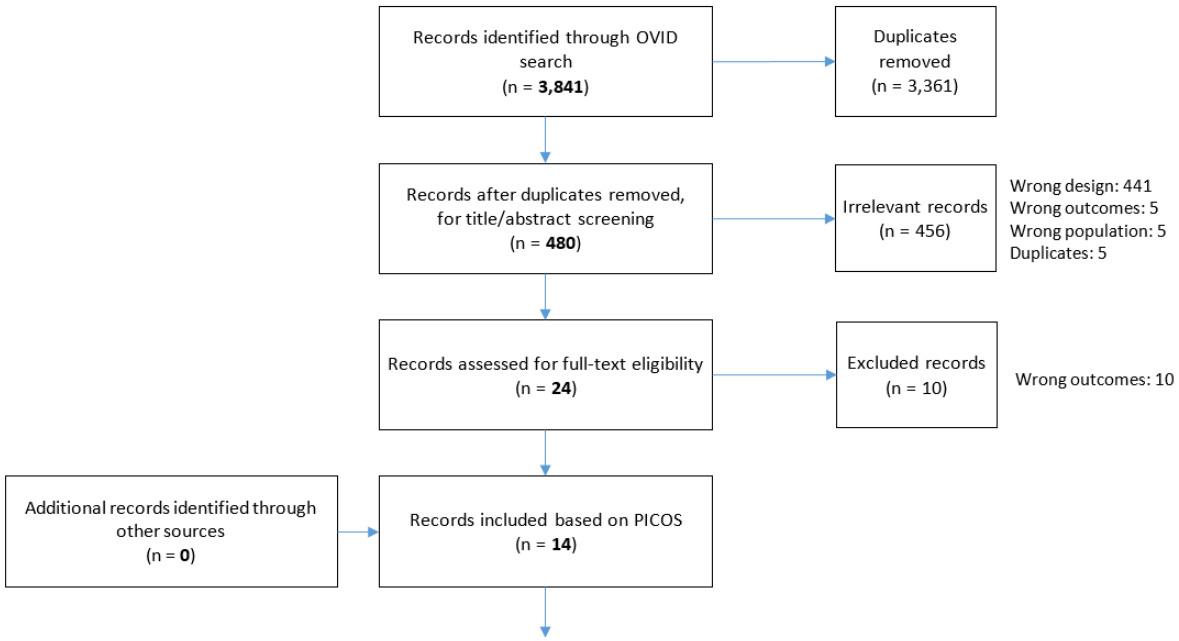
Figure 3: PRISMA statement: HRQoL SLR – May 2017



	Priority	QoL publications
1	BRAF inhibitors	12
2	IO	24
3	Other treatments	9
4	No specific treatment	18
5	Methodological papers, reviews	29

BRAF: B-Raf proto-oncogene, serine/threonine kinase; IO: Immuno-Oncology; QoL: Quality of Life

Figure 4: PRISMA statement: HRQoL SLR – Update April 2018



Priority		QoL publications
1	BRAF inhibitors	2
2	IO	5
3	Other treatments	0
4	No specific treatment	4
5	Methodological papers, reviews	3

BRAF: B-Raf proto-oncogene, serine/threonine kinase; IO: Immuno-Oncology; QoL: Quality of Life

In Denmark, the only BRAFi/MEKi combination treatment in use is Dabra+Tram [8], which is therefore the comparator of interest for this submission. In total, six records identified in the HRQoL SLR reported HRQoL data on three relevant RCTs investigating BRAFi, either as monotherapy or in combination with MEKi: COLUMBUS, COMBI-v, COMBI-d (Table 4).

Table 4. Relevant HRQoL studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
- Quality-of-Life (QoL) in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant Melanoma. Gogas, H et al. *Ann. Oncol.* Sep. 2017 [19]	**COLUMBUS**	NCT01909453	December 2013 – November 2017 (Completed)	1,2
- Analysis of patient-reported outcomes by disease progression status in patients (pts) with BRAF V600-mutant metastatic melanoma in the COMBI-d and COMBI-v trials. Robert, C et al. *Ann. Oncol. Conf. 41st Eur. Soc. Med. Oncol. Congr. ESMO.* 2016.* - Health-related quality-of-life (HRQOL) impact of dabrafenib (D) and trametinib (T) vs BRAF inhibitor (BRAFi) monotherapy by lactate dehydrogenase (LDH) in patients (pts) with BRAF V600-mutant melanoma. Grob, J. J et al. *Ann. Oncol. Conf.* 41st Eur. Soc. Med. Oncol. Congr. ESMO. 2016.* - Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma, Schadendorf, D et al Eur. *J. Cancer.* 2015.[20–22]	**COMBI-d**	NCT01584648	May 2012 –February 2016 (Completed)	1,2
- Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial', Grob, J. J et al. *Lancet Oncol.* 2015. - COMBI-v: Health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with BRAF V600 metastatic melanoma (MM). Grob, J. J et al. *Eur. J. Cancer.* 2015. - Analysis of patient-reported outcomes by disease progression status in patients (pts) with BRAF V600-mutant metastatic melanoma in the COMBI-d and COMBI-v trials. Robert, C et al. *Ann. Oncol. Conf. 41st Eur. Soc. Med. Oncol. Congr. ESMO.* 2016.*	**COMBI-v**	NCT01597908	June 2012 –July 2014 (completed)	1,2

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question
- Health-related quality-of-life (HRQOL) impact of dabrafenib (D) and trametinib (T) vs BRAF inhibitor (BRAFi) monotherapy by lactate dehydrogenase (LDH) in patients (pts) with BRAF V600-mutant melanoma. Grob, J. J et al. *Ann. Oncol. Conf. 41st Eur. Soc. Med. Oncol. Congr. ESMO*. 2016.[20,21,23,24]*				

** Pooled analysis of COMBI-v and COMBI-d trials*

4.3 Main characteristics of included studies

4.3.1 COLUMBUS

COLUMBUS was a 2-part, randomised, open-label, multicentre, Phase III study. As part 1 of the COLUMBUS trial provided the pivotal clinical evidence supporting the licensed indication of Enco+Bini 450, only evidence from COLUMBUS Part 1 has been included in this submission, as per the DMC protocol. The primary endpoint was progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Overall survival was assessed as a secondary outcome. Details of the study, including study type and design, randomisation, blinding, patient inclusion and exclusion criteria, data analyses and follow up, and baseline characteristics are summarised (Table 5).

Table 5. COLUMBUS: main study characteristics

Trial name	**COLUMBUS (CMEK162B2301)** Study Comparing Combination of LGX818 Plus MEK162 Versus Vemurafenib and LGX818 Monotherapy in BRAF Mutant Melanoma
NCT number	NCT01909453
Objective	**Part 1:** To determine whether treatment with Enco+Bini 450 prolongs PFS compared with vemurafenib in patients with BRAF V600-mutant locally advanced unresectable or metastatic melanoma **Part 2:** To further evaluate the contribution of Enco+Bini 450 to combination therapy by comparing a lower dose of encorafenib (300 mg QD) in combination with binimetinib to encorafenib 300 mg monotherapy *In line with the licensed indication (Enco+Bini 450), only evidence from COLUMBUS Part 1 has been included in this submission, as per the DMC protocol.*
Publications – title, author, journal, year	- Dummer et al., Results of COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant Melanoma, SMR, 2016. [25] - Gogas et al., Quality of Life in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib Plus Binimetinib vs Vemurafenib or Encorafenib Monotherapy in BRAF-Mutant Melanoma, ESMO, 2017. [19] - Arance et al., Hospitalization Rates in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant melanoma, ESMO, 2017. [26] - Dummer et al., Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial, The Lancet, 2018. [10] - Dummer et al., Overall survival in COLUMBUS: a phase III trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEMU) or ENCO in BRAF-mutant melanoma, ASCO, 2018. [11] - Gogas et al. Adverse events of special interest in the phase 3 COLUMBUS study. J Clin Oncol, 2018 [13] - Dummer et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial, Lancet Oncol, 2018 [27]
Study type and design	A 2-part, randomised, open-label, international, multicentre, parallel group, Phase 3 study. In Part 1 approximately 576 patients were to be randomised in a 1:1:1 ratio to one of three treatment arms:

	- Enco+Bini 450 arm: encorafenib 450mg once daily in combination with binimetinib 45mg twice daily - Encorafenib 300 arm: encorafenib 300mg once daily - Vemurafenib arm: vemurafenib 960mg twice daily Randomisation was stratified according to the following factors: - AJCC stage (IIIB + IIIC + IVM1a + IVM1b vs IVM1c) - ECOG PS (0 vs. 1) - Prior first-line immunotherapy (yes vs. no) after protocol amendment 2/BRAF mutation status (V600E vs. V600K) prior to protocol amendment 2 At protocol amendment 2 stage, stratification factors were modified such that prior first-line immunotherapy (yes vs. no) was added and BRAF mutation status (V600E vs. V600K) was removed. The BRAF mutation status was to be investigated as a covariate in the multivariate Cox-model and in a subgroup analysis if the primary endpoint was found to be significant. This was to ensure a balanced distribution among treatment arms of patients who had progressed on first-line immunotherapy and those with no prior treatment for locally advanced or metastatic melanoma. **Randomisation**: Each patient was assigned a unique patient number upon enrolment for pre-screening and randomisation numbers were generated to ensure that treatment assignment was unbiased and concealed from the Sponsor or designee's trial team. Prior to dosing, patients who fulfilled all inclusion/exclusion criteria were randomised via interactive response technology to one of the treatment arms; a patient randomisation list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomisation numbers, and these randomisation numbers were linked to the different treatment arms. **Blinding:** As this was an open-label study,* investigators and patients knew the study treatment assigned. To minimise bias, confirmation of progression had to be confirmed by independent review committee blinded to patient treatment assignment. Sponsor personnel responsible for data analysis and interpretation were also blinded to data that would systematically unblind patient treatment assignments until database lock for the primary analysis.

* An open-label design was chosen in the interests of patient safety, due to the characteristic MEKi toxicities, such as ocular side effects and raised blood creatine kinase, that would result in patients in the combination arm being functionally unblinded. In addition, treatment with vemurafen b is also associated with characteristic toxicities including photosensitivity, which again would result in unblinding of the study.

	Study phases: The study consisted of the following phases: pre-screening, screening and randomisation; treatment phase; end of treatment; and the follow-up period. • The treatment phase consisted of 28-day treatment cycles which continued until PD as determined by the BIRC, unacceptable toxicity, death, physician decision, early termination of the study, or discontinuation for any other reason (e.g. withdrawal of consent, lost to follow-up). • All patients were to have a safety follow-up visit 30 days after the last dose of study treatment. • Patients then had additional assessment visits depending on the reason for study drug discontinuation. • In the event of PD, patients had survival follow-up visits every 12 weeks to assess for survival and new antineoplastic treatment until death occurred. • In the event of treatment discontinuation for other reasons, patients continued to have tumour and patient reported outcome assessments, until progression, consent withdrawal, lost to follow-up or death. **Populations analysed:** The following populations were considered in the study: • Full Analysis Set (FAS): defined according to the ITT principle and consisted of all randomised patients. Patients were analysed according to the treatment and stratification factors they were assigned to at randomisation. Efficacy outcomes were primarily assessed using the FAS. • At the time of the primary PFS analyses, all patients randomised to Part 1 of the study were included and analyses based on data collected up to and including 19 May 2016. • Per-protocol Set (PPS): included all patients from the FAS who had no major protocol deviations and who received at least one dose of study medication. • Safety Set: included patients who received at least one dose of the study medication and had at least one valid post-baseline safety evaluation. Patients were analysed according to the study treatment they actually received, defined as the treatment received during the whole treatment period. This was the analysis set for all safety evaluations. Seven patients (5 patients in the vemurafenib arm and 2 patients in the Enco 300 arm) were randomised but did not receive study drug and were excluded from the PPS and the Safety Set.

Follow-up time	The median follow-up time for PFS per BIRC was 16.7 months for the Enco+Bini 450 arm and 14.4 months for the vemurafenib arm at the time of the primary analysis.
Population (inclusion and exclusion criteria)	Patients were male or female, at least 18 years of age with histologically confirmed locally advanced unresectable or metastatic BRAF V600E and/or V600K-mutant cutaneous melanoma or unknown primary melanoma (stage IIIB, IIIC or IV per AJCC) as determined by a Sponsor-designated central laboratory(ies), and previously untreated (treatment naïve) or had progressed on or after prior first-line immunotherapy for advanced or metastatic disease. Prior systemic treatment in the adjuvant setting was allowed, except for the administration of BRAFi or MEKi. Patients were also to have at least one measurable lesion as per RECIST version 1.1, an ECOG PS of 0–1 and adequate organ and cardiac function, including left ventricular ejection fraction ≥ 50% by cardiac imaging. Patients with any untreated CNS lesion, uveal and mucosal melanoma, a history of leptomeningeal metastases, history or current evidence of, or current risk factors for retinal vein occlusion, or a history of Gilbert's syndrome were excluded.
Intervention	**Intervention:** • Enco+Bini 450 arm: encorafenib 450 mg QD plus binimetinib 45 mg BID (N=192) **Comparators:** • Vemurafenib arm: vemurafenib 960 mg BID monotherapy (N=191) • Encorafenib 300 mg arm: encorafenib 300 mg QD monotherapy (N=194)
Baseline characteristics	The treatment arms were well balanced with regard to relevant demographic and baseline characteristics including patient age, gender, race, ECOG PS, and disease stage at study entry. The median age was 57.0 years in the Enco+Bini 450 arm and 56.0 years in the vemurafenib arm respectively. A similar proportion of men was recruited between the treatment arms (59.9% and 58.1% respectively). The median weight was also close between Enco+Bini 450 arm and vemurafenib arm (78.1 vs 78.7 kg), while the median body surface area was identical (1.9 m^2 each). Respectively 29.2% of patients from the Enco+Bini 450 arm and 26.7% patients from the vemurafenib had ECOG PS 1, while the remaining patients had an ECOG PS 0. The majority of patients (Enco+Bini 450: 64.1%; vemurafenib: 65.4%) were Stage IV M1C at study entry, and of those Stage IV M1C patients, more patients had normal LDH levels than elevated LDH levels. At baseline, the median LDH and the percentage of patients with elevated LDH was similar among the treatment arms, with 28.6% and 27.2% of patients classified as having high LDH, for Enco+Bini 450 and vemurafenib respectively.

	The percentage of patients who had received prior antineoplastic therapies overall was similar across the treatment arms (82.3% vs 86.4% respectively).
Primary and secondary endpoints	The primary endpoint was progression-free survival (PFS), defined as the time from the date of randomisation to the date of the first documented disease progression or death due to any cause, whichever occurs first; determined based on tumour assessment (RECIST v1.1) as per BIRC and survival information. The local investigator's assessments were used as supportive analyses. Secondary endpoints were overall survival, objective response rate, time to response, duration of response, disease control rate, health-related quality of life (HRQoL) as assessed by FACT-M, QLQ-C30 and EQ-5D, and safety.
Method of analysis	Primary efficacy analyses were conducted using the FAS, with supportive analyses performed using the per-protocol set (PPS). The BIRC assessments were used for the main analyses of PFS, best overall response, overall response rate, time to objective response, duration of response and disease control rate. Analyses on the local assessments were presented for these endpoints for sensitivity analysis purposes. A hierarchical approach was used to control for the type I error rate, with formal OS testing to be performed only if the primary and key secondary PFS analysis was statistically significant.
Subgroup analyses	For PFS and OS, subgroup analyses were to be performed for each of the baseline stratification factors and other relevant baseline variables provided at least 10 patients were available in the considered sub-group.
Data sources	**May 2016:** CSR [28]; Dummer et al 2018 [10]; Gogas et al 2017 ESMO [19]; Gogas et al 2018 ASCO [13] **November 2016 safety update:** EMA MAA safety update [29] **November 2017 efficacy update:** CSR OS addendum November 2017 data cut-off [30]; OS topline report [31]; Efficacy update report 7 November 2017 data cut-off [32]; Dummer et al 2018 ASCO [11] **Post-hoc analyses reports:** Post-hoc analyses reports [33,34]

Abbreviations: AJCC: American Joint Committee on Cancer; BIRC, blinded independent review committee; BRAF: B-Raf proto-oncogene, serine/threonine kinase; BRAFi: BRAF inhibitor; CNS: central nervous system; CSR: clinical study report; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; HRQoL: Health-related Quality of Life; IRT: interactive response technology; ITT: intention-to-treat; LDH: lactate dehydrogenase; MAA: marketing authorisation application; MEKi: Mitogen/Extracellular signal-regulated kinase inhibitor; OS: overall survival; PD, progressive disease; PFS: progression-free survival; QD: once-daily

4.3.2 COMBI-d

COMBI-d was a double-blind, phase III study in which 423 patients with BRAF Val600Glu or Val600Lys mutation-positive unresectable stage IIIC or stage IV melanoma were randomised to receive dabrafenib 150 mg twice daily + trametinib 2 mg once daily or dabrafenib only. The primary endpoint was PFS (per RECIST 1.1). Details of the study, including study type and design, randomisation, blinding, patient inclusion and exclusion criteria, data analyses and follow up, and baseline characteristics are summarised (Table 6). As of September 2018, the study was still ongoing.

Table 6: COMBI-d: main study characteristics

Trial name	**COMBI-d** A Study Comparing Trametinib and Dabrafenib Combination Therapy to Dabrafenib Monotherapy in Subjects With BRAF-mutant Melanoma
NCT number	NCT01584648
Objective	To determine whether treatment with dabrafenib + trametinib prolongs PFS compared with dabrafenib monotherapy as assessed by the investigator
Publications – title, author, journal, year	- Long et al., Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma, NEJM, 2014. [16] - Long et al., Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial, The Lancet, 2015. [18] - Long 2017, Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Annals of Oncology, 2017. [17]
Study type and design	A two-arm, double-blinded, randomised, phase III study comparing dabrafenib (GSK2118436) and trametinib (GSK1120212) combination therapy to dabrafenib administered with a trametinib placebo (dabrafenib monotherapy). Subjects with histologically confirmed cutaneous melanoma that is either Stage IIIC (unresectable) or Stage IV, and BRAF V600E/K mutation positive were screened for eligibility. Subjects who have had prior systemic anti-cancer treatment in the advanced or metastatic setting were not eligible although prior systemic treatment in the adjuvant setting was allowed. Patients were randomly assigned in equal ratio (1:1). Patients were stratified by LDH level (> the ULN versus less than or equal to the ULN) and BRAF mutation status (V600E versus V600K). Crossover was not permitted at the time of disease progression. As of September 2018, the study was still ongoing.
Follow-up time	At the primary analysis, the median follow-up time was 9 months (range, 0 to 16). At the latest data cut-off (February 2016), patients who were alive had >36 months of follow-up from time of randomization.
Population (inclusion and exclusion criteria)	Eligible patients had histologically confirmed, unresectable stage IIIC or stage IV metastatic melanoma with BRAF V600E or V600K mutations, as determined by means of an investigational use-only polymerase-chain-reaction assay (ThxID BRAF Assay, bioMérieux) performed at a

	central reference laboratory. Patients were not eligible if they had previous systemic anticancer therapy (including BRAFi or MEKi). Patients with brain metastases that had been definitively treated and stable for at least 12 weeks were eligible to participate.
Intervention	423 patients were randomised in a 1:1 ratio to one of the following treatment arms: • Combination therapy: dabrafenib 150 mg twice daily + trametinib 2 mg once daily (n=211) • Monotherapy: dabrafenib 150 mg twice daily and trametinib placebo (n=212)
Baseline characteristics	Baseline characteristics were similar in the two study groups. The median age was 55.0 years in the combination arm and 56.5 years in the monotherapy arm respectively. A similar proportion of men was recruited between the treatment arms (53% and 54% respectively). Respectively 26% of patients from the combination arm and 29% patients from the monotherapy arm had ECOG PS 1, while the remaining patients had an ECOG PS 0. The majority of patients (combination: 67%; monotherapy: 65%) were Stage IV M1C at study entry. At baseline, the percentage of patients with elevated LDH was similar among the treatment arms, with 63% and 67% of patients respectively. The percentage of patients who had received prior immunotherapy was similar across the treatment arms (27% vs 29% respectively).
Primary and secondary endpoints	The primary endpoint was investigator-assessed PFS, defined as the time from randomization until radiologic disease progression or death from any cause. Tumour assessments were conducted according to RECIST, version 1.1, The secondary endpoints were overall survival, response rate, response duration, safety, and pharmacokinetics.
Method of analysis	The study was initially designed with a power of more than 90% to detect a 41% reduction in the risk of disease progression or death (HR 0.59) in the dabrafenib–trametinib group, as compared with the dabrafenib-only group, at a one-sided type I error rate of 0.025. The study was overenrolled by approximately 24% (423 actual enrolees vs. the target of 340). To increase the precision of the median PFS estimate in the combination group, the final analysis was planned after 193 events had occurred, which maintained the same ratio of events to patients as originally planned. As a result, the power increased from 90% to 95%. A prespecified interim analysis of overall survival was planned at the time of the analysis of PFS. The stopping boundary for the interim analysis of overall survival (OS) was a two-sided alpha level of less than 0.00028. A final OS analysis was conducted when 70% of the patients who underwent randomization have died or been lost to follow-up. An independent central review committee whose members were unaware of study-group assignments reviewed radiologic findings on which a sensitivity analysis of PFS was based. No interim analyses were performed for efficacy or futility with respect to the primary endpoint.

	Efficacy was determined in all patients in the intention-to-treat population; safety analyses were performed in all patients who received at least one dose of a study drug. Treatment beyond progression was defined as the receipt of a study drug more than 15 days after radiologic progression, as defined by RECIST.
Subgroup analyses	Subgroup analyses included the stratified factor (BRAF mutation and LDH level [> the ULN versus less than or equal to the ULN]). Post hoc subgroup analyses were performed with the use of an unstratified log-rank test for tumour stage, ECOG PS, visceral disease, number of distant sites, sex and age (</> 65 years).

Abbreviations: BRAF: B-Raf proto-oncogene, serine/threonine kinase; BRAFi: BRAF inhibitor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; LDH: lactate dehydrogenase; MEKi: Mitogen/Extracellular signal-regulated kinase inhibitor; OS: overall survival; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal

4.3.3 COMBI-v

This was an open-label, phase III trial in which 704 patients with metastatic melanoma with a BRAF V600 mutation were randomly assigned to receive either a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or vemurafenib (960 mg twice daily) orally as first-line therapy. The primary endpoint was overall survival. As of September 2018, the study was still ongoing. Details of the study, including study type and design, randomisation, blinding, patient inclusion and exclusion criteria, data analyses and follow up, and baseline characteristics are summarised (Table 7).

Table 7: COMBI-v: main study characteristics

Trial name	**COMBI-v** Dabrafenib Plus Trametinib vs Vemurafenib Alone in Unresectable or Metastatic BRAF V600E/K Cutaneous Melanoma
NCT number	NCT01597908
Objective	To determine whether treatment with dabrafenib + trametinib prolongs PFS compared with vemurafenib monotherapy as assessed by the investigator
Publications – title, author, journal, year	- Robert et al., Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib, NEJM, 2015 [14] - Robert et al. Three-year estimate of overall survival in COMBI-v, a randomised phase 3 study evaluating first-line dabrafenib (D)+ trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. Ann. Oncol. 27 (2016) [15] - Grob et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol. 2015 [23]
Study type and design	A two-arm, open-label, randomised, phase III study comparing dabrafenib (GSK2118436) and trametinib (GSK1120212) combination therapy to vemurafenib. Subjects with histologically confirmed cutaneous melanoma that is either stage IIIc (unresectable) or stage IV, and BRAF V600E/K mutation positive were screened for eligibility. Subjects who have had prior systemic anti-cancer treatment in the advanced or metastatic setting were not eligible although prior systemic treatment in the adjuvant setting was allowed. Patients were randomly assigned in equal ratio (1:1). Patients were stratified by LDH level (> the ULN versus less than or equal to the ULN) and BRAF mutation status (V600E versus V600K). Crossover was prohibited until the independent data and safety monitoring committee recommended stopping the study early for efficacy. After the recommendation, the study protocol was amended to allow patients in the vemurafenib group to cross over to the combination-therapy group. As of September 2018, the study was still ongoing.
Follow-up time	At the primary analysis, the median follow-up time was 11 months in the combination group and 10 months in the combination group.

Population (inclusion and exclusion criteria)	The presence of BRAF V600E or V600K mutations was centrally determined with the investigational use of the THxID BRAF assay (bioMérieux). Additional key eligibility criteria were measurable disease, according to the RECIST, version 1.1,15 and an ECOG PS of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms and higher numbers reflecting greater disability).16 Patients who had undergone treatment for brain metastases with no increase in lesion size for at least 12 weeks were eligible for enrolment.
Intervention	704 patients were randomized in a 1:1 ratio to one of the following treatment arms: -Combination therapy: dabrafenib 150 mg twice daily + trametinib 2 mg once daily (n=352) -Monotherapy: vemurafenib 960 mg twice daily (n=352)
Baseline characteristics	Known prognostic measures were well balanced in the two groups except for sex (59% men in the combination arm vs. 51% in the vemurafenib arm). The median age was 55 years in the combination arm and 54 years in the monotherapy arm respectively. Respectively 29% of patients from the combination arm and 30% patients from the monotherapy arm had ECOG PS 1, while the remaining patients had an ECOG PS 0. The majority of patients (combination: 63%; monotherapy: 59%) were Stage IV M1C at study entry. At baseline, the percentage of patients with elevated LDH was similar among the treatment arms, with 34% and 32% of patients respectively. The percentage of patients who had received prior immunotherapy was slightly lower in the combination arm (17%) compared to the monotherapy arm (26%).
Primary and secondary endpoints	The primary endpoint was OS for subjects receiving the combination therapy compared with those receiving vemurafenib. Tumour assessments were conducted according to RECIST, version 1.1, Secondary end points included progression-free survival, overall response rate, duration of response, and safety.
Method of analysis	The Kaplan–Meier method to estimate overall survival and PFS. Between-group comparisons were evaluated using a logrank test that was stratified for the BRAF mutation status (V600E vs. V600K) and the baseline level of lactate dehydrogenase (LDH) (above the upper limit of the normal range vs. the upper limit of the normal range or less). It was estimated that 288 events would be required to detect a hazard ratio for death of 0.675 with an alpha level of 0.05 (i.e., an increase in median overall survival from 13.5 months in the vemurafenib group to 20 months in the combination-therapy group). Overall survival was defined as the time from randomisation until death from any cause. A preplanned interim analysis for overall survival was to be conducted when 202 of 288 events that were required for the final analysis (70%) had been observed. Owing to the inherent lag in data entry, the actual number of deaths was 222 at the time of the interim analysis. Per protocol, efficacy boundaries were adjusted on the basis of the actual number of deaths at the time of the interim analysis. The data and safety monitoring committee used the adjusted stopping boundaries (two-sided P<0.0214 for the efficacy analysis and P>0.2210 for the futility analysis) to review

	the interim data. The committee recommended stopping for efficacy. As such, the interim summary is considered to be the final analysis of overall survival.
Subgroup analyses	Subgroup analyses included the stratified factor (BRAF mutation and LDH level [> the ULN versus less than or equal to the ULN]). Post hoc subgroup analyses were performed with the use of an unstratified log-rank test for *BRAF* mutation (V600K, V600E), tumour stage, ECOG PS, baseline LDH, number of disease sites, sex and age (</≥ 65 years).

Abbreviations: BRAF: B-Raf proto-oncogene, serine/threonine kinase; BRAFi: BRAF inhibitor; ECOG PS: Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; OS, overall survival; PFS: progression-free survival; RECIST: Response Evaluation Critera in Solid Tumors; ULN, upper limit of normal

5. Clinical question

5.1 Clinical question

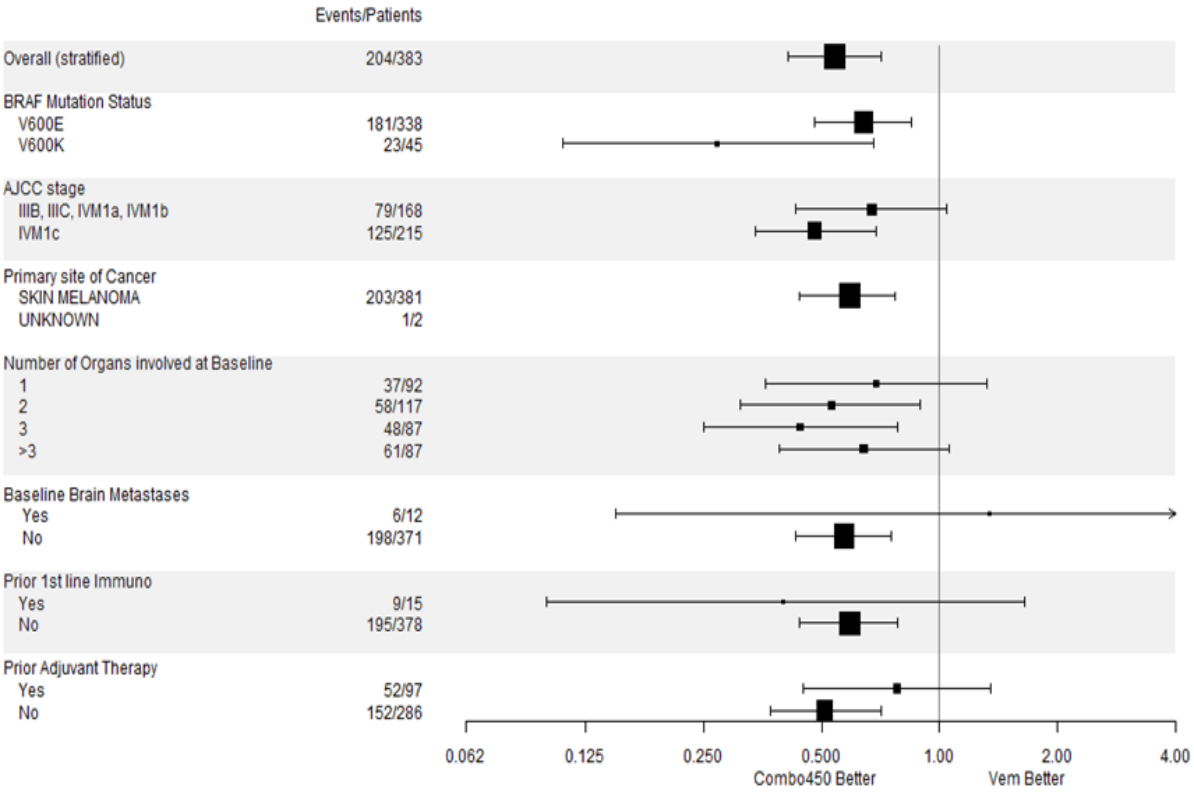
What clinical value does encorafenib offer in combination with binimetinib compared with dabrafenib in combination with trametinib in patients with non-resectable or metastatic melanoma with BRAF V600 mutation, who are candidates for treatment with a BRAF-MEK inhibitor?

Results are presented based on the licensed indications for Enco+Bini 450 and Dabra+Tram, with no differentiation between patients in the first line and second line treatment setting for metastatic melanoma. Deviation from the Medicine Council's protocol in this case was deemed appropriate due to the availability of evidence as outlined below.

- In the COMBI-d and COMBI-v trials of Dabra+Tram, based on the eligibility criteria, patients who had prior systemic anti-cancer treatment in the advanced or metastatic setting were excluded from enrolment.
- In the Enco+Bini 450 arm of the COLUMBUS trial, only six patients in the Enco+Bini 450 arm and three patients in the vemurafenib arm received prior immunotherapy (ipilimumab or anti-PD1/PDL1) for metastatic disease (Figure 5).

As reflected in the ESMO guidelines, due to the lack of long-term data for BRAFi/MEKi therapies following immunotherapy, it is not possible to make a comparison between Enco+Bini 450 and Dabra+Tram therapy for patients with non-resectable or metastatic melanoma in the second line setting. However, emerging data do suggest that BRAF inhibition is effective following immunotherapy, and checkpoint inhibitors are still effective in patients who have progressed on kinase-inhibitor therapy [35].

Figure 5: Forest plot of PFS based on BIRC for Enco+Bini 450 versus vemurafenib – FAS, Part 1, data cut-off 19 May 2016



Abbreviations: AJCC, American Joint Committee on Cancer; BIRC, Blinded Independent Review Committee; BRAF, B-Raf proto-oncogene, serine/threonine kinase; Combo450, encorafenib in combination with binimetinib; CI, confidence interval; FAS, full analysis set; PFS, progression-free survival;
The CI was truncated for the subgroups of "yes" baseline brain metastases, Australia and "yes" Japanese as they continued beyond the limits of the x-axis.
Notes: Figure depicts patients with prior immunotherapy in both adjuvant and metastatic settings.
The hazard ratio is obtained from an unstratified Cox model.
Source: CSR [28]*, Dummer et al 2018* [10].

In addition, results presented for all safety critical effect measures are based on adverse events (AEs), rather than adverse reactions, as specified by the Medicine Council. In this case, deviation from the Medicine Council's protocol was deemed appropriate based on the availability of evidence on safety outcomes for Enco+Bini 450 and Dabra+Tram [10,14,17]. In the COLUMBUS, COMBI-v and COMBI-d trials tolerability was assessed by the incidence of AEs, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [36], and not adverse reactions. As such all safety critical effect measures described in this application are based on AEs. In COLUMBUS, an AE was defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical condition(s) that occurred after the patient had signed the informed consent form.

5.2 Presentation of relevant studies

The included studies are broadly similar in terms of study design and population, with regards to mutation status, performance status and prior therapy. Notable differences were:

- COMBI-v proposed crossover from vemurafenib to Dabra+Tram after first preliminary analysis (pre-specified in protocol)
- COLUMBUS and COMBI-v had an open label design.
- COLUMBUS study used a blinded independent review committee (BIRC) to assess the PFS (primary endpoint) and the response rates to minimise any possible bias in the study. BIRC assessment in this context is thought to reduce risk of bias of the open label design in that the assessment is done by a blinded independent review committee rather than the investigator.

5.3 Results per study

5.3.1 COLUMBUS study

An overview of endpoints as per the Medicines Council's protocol is provided with the study characteristics in section 4.3.1.

The pivotal, two-part, phase III COLUMBUS trial provides the key evidence on the clinical efficacy, safety and tolerability of Enco+Bini 450 compared with vemurafenib 960 mg twice-daily monotherapy and encorafenib 300 mg once-daily monotherapy in patients with locally advanced unresectable or metastatic BRAF V600 mutation-positive melanoma.

Part 1 was designed to evaluate the use of Combo 450 (licensed indication). Part 2 was designed to further define the contribution of binimetinib to the combination using a lower encorafenib dose of 300 mg once-daily. Encorafenib 300 mg is not licensed for metastatic melanoma; therefore, Part 2 of the COLUMBUS trial is not relevant for the appraisal of Combo 450 in metastatic melanoma.

PFS, OS and treatment responses presented in this section use the most recent study cut-off date of November 2017. The safety analysis represents the data from the clinical study report (CSR) and the primary trial publication by Dummer et al, 2018 (Data cut-off 19 May 2016) [10,28]. The narrative on selected AEs of interest represents the data presented to the European Medicines Agency (EMA) as part of the marketing authorisation application for Enco+Bini 450, based on a data cut-off of 9 November 2016, which is also published in both European Public Assessment Reports (EAPRs) for Braftovi® and Mektovi® [29,37,38]. HRQoL outcomes are presented using the primary cut-off date of May 2016 as these outcomes were not updated after that date. The data sources corresponding to each of the data cut-off dates are presented in Table 8.

Table 8: COLUMBUS (Study CMEK162B2301) data cut-off dates and associated data sources

Data cut-off	Data source
May 2016	CSR [28]; Dummer et al 2018 [10]; Gogas et al 2017 ESMO [19]
November 2016 safety update	EMA MAA safety update [29], EPAR Braftovi®/ Mektovi® [37,38]
November 2017 efficacy update	CSR OS addendum November 2017 data cut-off [30]; OS topline report [31]; Efficacy update report 7 November 2017 data cut-off [32]; Dummer et al 2018 ASCO [11] Dummer et al Lancet Oncol, 2018 [27]
Post-hoc analyses reports	Post-hoc analyses reports [33,34]

Abbreviations: CSR, clinical study report; EMA, European Medicines Agency; MAA, marketing authorisation application

At the time of the most recent data cut-off (i.e. 07 November 2017), 22% of patients in the Enco+Bini 450 arm, 12% in the encorafenib arm, and 7% in the vemurafenib arm were still on treatment.

The results of the COLUMBUS study are presented in Table 9 and summarised below.

Table 9: Results of COLUMBUS

Trial name:	COLUMBUS (CMEK162B2301)							
NCT number:	NCT01909453							
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect	Estimated relative difference in effect			Description of methods used for estimation
				Difference	Hazard ratio	95% CI	P value	
OS Median, months	Enco+Bini 450	192	33.6 (24.4–39.2)	16.7 months	0.61	0.47–0.79	<0.0001	The survival rates were based on the KM estimator. The HR was based on a Cox proportional hazards model with adjustment for stratification, and study arm. Population: FAS, Part 1 Data cut-off 7 November 2017 [11,27]
	Vemurafenib	191	16.9 (14.0–24.5)					
AEs – Patient with G3-4 events n (%)	Enco+Bini 450	192	111 patients (57.8%)	-5.6%	NR			Adverse events were graded by the site investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) Population: Safety set, Part 1 Data cut-off: May 2016 [10]
	Vemurafenib	186	118 patients (63.4%)					
AEs – Patients with treatment discontinuation due to AE n (%)	Enco+Bini 450	192	24 patients (12.5%)	-4.2%	NR			All grade AEs Population: Safety set, Part 1 Data cut-off: May 2016 [10]
	Vemurafenib	186	31 patients (16.7%)					
PFS-BIRC Median, months	Enco+Bini 450	192	14.9 (11.0–20.2)	7.6 months	0.51	0.39–0.67	<0.0001	The median survival was based on the KM estimator. The HR was based on a Cox proportional hazards model with adjustment for stratification, and study arm Population: FAS, Part 1 Data cut-off: November 2017 [11]
	Vemurafenib	191	7.3 (5.6–7.9)					
FACT-M	[redacted]	[redacted]		NR	[redacted]	[redacted]	[redacted]	

Trial name:	COLUMBUS (CMEK162B2301)							
NCT number:	NCT01909453							
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect	Estimated relative difference in effect			Description of methods used for estimation
				Difference	Hazard ratio	95% CI	P value	
Time to definitive 10% deterioration Median, months								Time to definitive 10% deterioration on the FACT-M melanoma subscale was analysed using the Kaplan-Meier method. Cox regression models, stratified by randomisation stratification factors, were used to estimate the HRs and 2-sided 95% CI. Data cut-off: May 2016 [28]
QLQ-C30 GH Time to definitive 10% deterioration Median, months				NR				Time to definitive 10% deterioration on EORTC QLQ-C30 global health status scale was analysed using the Kaplan-Meier method. Cox regression models, stratified by randomisation stratification factors, were used to estimate the HRs and 2-sided 95% CI. Data cut-off: May 2016 [28]
ORR-BIRC % (95% CI)	Enco+Bini 450	192	63.5% (56.3–70.4)	22.7%	NR			ORR was defined as the proportion of patients with best overall response of CR or PR. ORR was presented by treatment arm along with exact 95% CI. Population: FAS, Part 1 Data cut-off: November 2017 [11]
	Vemurafenib	191	40.8% (33.8–48.2)					
ORR – brain metastasis	NR							NA

Trial name:	COLUMBUS (CMEK162B2301)							
NCT number:	NCT01909453							
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect	Estimated relative difference in effect			Description of methods used for estimation
				Difference	Hazard ratio	95% CI	P value	
Duration of response- BIRC Median, months	Enco+Bini	192	18.6 (12.7–24.1)	6.3 months	NR	NR	NR	DOR was calculated as the time from the date of first documented response (CR or PR) to the first documented progression or death due to underlying cancer. In case of no event, the patient was censored at the date of last adequate tumour assessment. DOR was estimated for responders. Population: FAS, Part 1 Data cut-off: November 2017[11]
	Vemurafenib	191	12.3 months (6.9–14.5)					

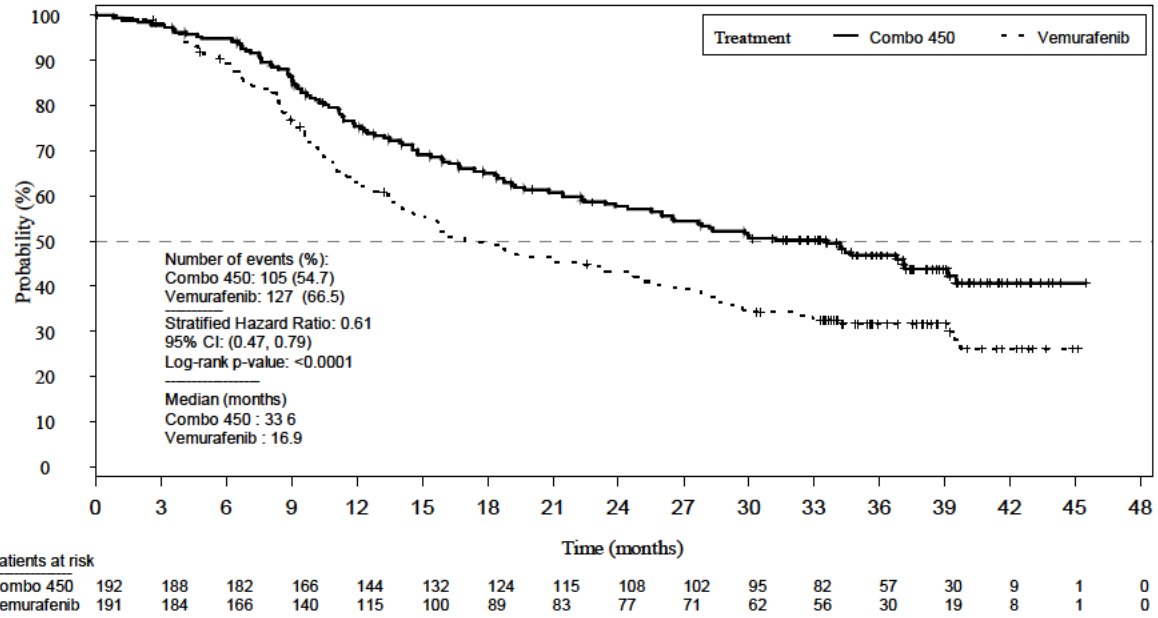
Abbreviations: AEs: adverse event(s): BIRC: Blinded Independent Review Committee; CR: complete response; CI: confidence interval; DOR: duration of response; EORTC: European Organization for Research and Treatment of Cancer; FACT-M: Functional Assessment of Cancer Therapy; FAS: full analysis set; GH: Global Health; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; QLQ-C30: Core Quality of Life Questionnaire; NA: not applicable; NE: not estimated; NR, not reported; PR: partial response

5.3.1.1. Critical effect measures summary

Survival

Median overall survival was twice as prolonged with Enco+Bini 450 compared to vemurafenib monotherapy (33.6 months vs. 16.9 months). A 39% reduction in the risk of death was observed in patients treated with Enco+Bini 450 compared to those treated with vemurafenib (HR: 0.61, 95% CI: 0.47, 0.79; p<0.0001); (Figure 6) [11].

Figure 6: Kaplan-Meier Plot of overall survival, Combo 450 vs. Vemurafenib (FAS, Part 1)



Abbreviations: CI: confidence interval. Source: Dummer et al. 2018 [11].

Sensitivity analyses of OS based on alternate stratification factors and analysis sets also yielded results consistent with the base case results [10].

Adverse events

The safety set in COLUMBUS (part 1) included 192 patients treated with Enco+Bini 450 and 192 patients treated with vemurafenib who received at least one dose of study drug. A lower percentage of patients in the Enco+Bini 450 arm, as compared with the vemurafenib arms, experienced at least one Grade 3–4 AE[2]. The rates of AEs and Grade 3 or 4 AEs leading to treatment discontinuation were similar across the three treatment groups [10] (Table 13).

[2] Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events_v4.03 [36]

Known adverse events

In addition to the safety set from COLUMBUS, pooled safety data supporting the marketing authorisation application for Enco+Bini 450 was derived from 274 patients with BRAF V600 mutation-positive metastatic melanoma enrolled at or randomised to a dose of encorafenib 450mg QD in combination with binimetinib 45mg BID, across three clinical trials [37,38]:

- COLUMBUS, Part 1 (as described in Section 4.3.1)
- LOGIC-2 (Study CLGX818X2109), Part A (a phase 2 study presented in the regulatory submission to the EMA to provide supportive efficacy evidence for the anticipated indication for Enco+Bini 450)
- Study CMEK162X2110 (Phase Ib/II multi-centre, open-label study, in adult patients who were previously naïve to BRAFi, either as monotherapy or in combination with a MEKi).

A narrative of characteristic BRAFi/MEKi AEs, based on the COLUMBUS study and the pooled safety set described above is provided in the section below.

Characteristic toxicities associated with BRAFi/ MEKi combination therapies were generally manageable, reversible, and infrequently associated with treatment discontinuation with Enco+Bini 450, and no serious unexpected AEs of special interest were observed [13]. In clinical trials, pyrexia has been observed in 51–53% of patients treated with Dabra+Tram [14,16], and photosensitivity observed in 48% of patients treated with vemurafenib + cobimetinib [39]; incidence of these AEs (any grade) in Enco+Bini 450 (pooled safety set, n=274) were 17.2% and 4.0%, respectively [37,38]. In an interview with Danish physicians, pyrexia was stated as the most common treatment-related AE leading to hospitalisation for Dabra+Tram, seen in 10-20% of treated patients; additionally they indicated that, approximately 5% of patients treated with Dabra+Tram require a dose reduction due to cardiac AEs [40].

Evidence from the COLUMBUS trial relating to AEs of special importance is further detailed below:

- *Pyrexia:* In COLUMBUS (Part 1) safety set, rates of pyrexia[3] (all grades) were experienced by a lower proportion of patients in the Enco+Bini 450 (18.2%;) group than in the vemurafenib group (29.6%). In the pooled safety set for Enco+Bini 450 (n=274), pyrexia (all grades) occurred in 17.2% of patients, with grade 3/4 events occurring in 2.9% of patients *[37,38]*.

- *Photosensitivity and radiotherapy:* In COLUMBUS (Part 1), photosensitivity[4] (all grades) occurred in 9/192 (4.7%) of patients in the Enco+Bini 450 group and 70/186 (37.6%) in the vemurafenib group. In the Enco+Bini 450 group, all events were grade 1 or 2, with the exception of one grade 3 event *[37]*. In the pooled safety set, photosensitivity was observed in 4.0%

[3] Includes pyrexia, body temperature increased, hyperpyrexia, hyperthermia
[4] Includes photosensitivity reaction, solar dermatitis

(11/274) of patients. Most events were Grade 1-2, with Grade 3 reported in 0.4 % (1/274) of patients and no event led to discontinuation. Dose interruption or dose modification was reported in 0.4 % (1/274) of patients [37,38].

In consideration of the half-life (terminal half-life of 3 to 4 hours) of encorafenib, in order to reduce possible skin toxicity during and after radiotherapy, it is recommended that all patients requiring palliative radiotherapy and/or stereotactic radiotherapy should interrupt treatment for at least five half-lives (i.e. interruption of approximately two days for Enco+Bini 450) prior to and after radiotherapy, or after having recovered from side effects of such a procedure [28].

- *Left ventricular dysfunction:* In the pooled safety set for Enco+Bini 450, left ventricular dysfunction (LVD)[5] was reported in 8.4%% (23/274) of patients. Grade 3 events occurred in 1.1 % (3/274) of patients. LVD led to treatment discontinuation in 0.4% (1/274) of patients and led to dose interruptions or dose reductions in 6.6 % (18/274) of patients. LVD was generally reversible following dose reduction or dose interruption [37].

- *Retinopathy:* Retinopathy is a known class effect of MEK inhibitors (Summary of Product Characteristics [SmPC] Binimetinib, see Appendix D, section D.2). Thus, the COLUMBUS trial specifically assessed this AE as a secondary safety endpoint. Retinopathy (all grades; excluding retinal vein occlusion) occurred in 144/274 (52.6%) of patients in the pooled Enco+Bini 450 group. Grade 3 events occurred not very frequent (2.2%) and most of the events were transient, self-limiting and reversible. The proposed recommendations regarding management and dose modification were acceptable [37].

Conclusions on safety

The safety data demonstrates that Enco+Bini 450 is generally well tolerated with a differentiated safety profile in patients with BRAF V600-mutant melanoma. Based on the COLUMBUS study, Enco+Bini 450 has a tolerability profile that is favourable compared with vemurafenib, as demonstrated by lower incidence of Grade 3 or 4 AEs, fewer AEs requiring dose interruption or modification and fewer discontinuations due to AEs. Common BRAFi/MEKi toxicities were generally manageable, reversible, and infrequently associated with treatment discontinuation with Enco+Bini 450, and no serious unexpected AEs of special interest were observed.

5.3.1.2. Important effect measures summary

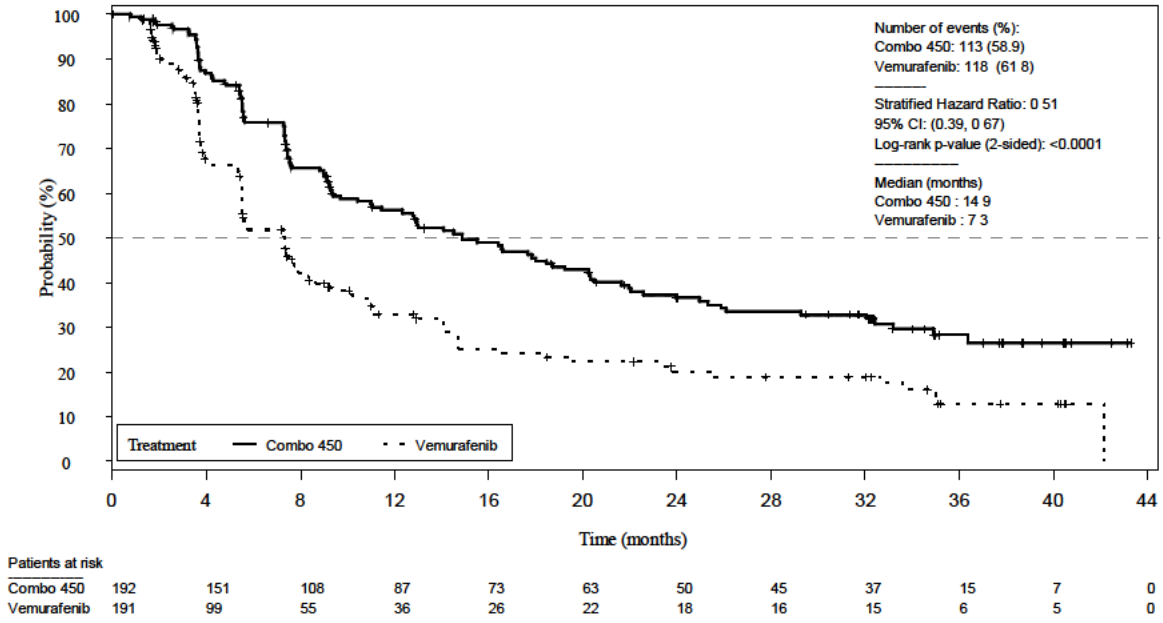
Progression-free survival

The pivotal COLUMBUS trial showed that the median PFS was twice as prolonged with Enco+Bini 450 compared to vemurafenib 960 mg twice daily (14.9 months vs. 7.3 months), thereby providing statistically

[5] Includes ejection fraction decreased, left ventricular dysfunction, and ejection fraction abnormal

significant and clinically relevant improvement in progression free survival (HR: 0.51; 95% CI: 0.39, 0.67, p<0.0001) [11] (Figure 7).

Figure 7: Kaplan-Meier estimate of PFS Based on BIRC – Combo 450 vs. vemurafenib - (FAS, Part 1)



Abbreviations: BIRC: blinded independent review committee; CI: confidence interval; FAS: full analysis set; PFS: progression-free survival; vs.: versus. Source: COLUMBUS Efficacy Updates November 2017 cut-off [32] Figure 14.2-1.1.1a

Health-related Quality of Life

Based on the longitudinal mixed model repeat measures (MMRM) analyses, treatment with Enco+Bini 450 was associated with higher post-baseline score estimates, suggesting clinically meaningful HRQoL gains with Enco+Bini 450 compared with monotherapy: versus vemurafenib (Functional Assessment of Cancer Therapy-Melanoma [FACT-M] melanoma scale [redacted]; EQ-5D index score [redacted]; Core Quality of Life Questionnaire (QLQ-C30) global health status [redacted] Compared with vemurafenib, the minimal clinically important difference of 2 points *[41]* was reached at all visits except Week 95 for the FACT-M melanoma subscale and the QLQ-C30 minimal clinically important difference of 5 points *[42]* was reached at all visits except Weeks 48 and 72 for the QLQ-C30 global health status score. Overall, the difference between arms reached the minimal clinically important difference in favour of Enco+Bini 450 at more than 80% of post-baseline assessments, in a large range of QLQ-C30 domains including pain, insomnia, appetite loss, fatigue and diarrhoea symptoms, global health, role and social functioning scores, as well as the FACT-M melanoma subscale. The difference in EQ-5D-5L index score was numerically in favour of the Enco+Bini 450 arm versus vemurafenib, although the minimal clinically important difference (≥0.08 points) *[43]* was only reached at the last visit (Table 10); the minimal clinically important difference for the EQ-VAS (≥7 points) was not reached between Cycle 3 and 25 [33].

Table 10: Mean score change from baseline at each time-point, EQ-5D-5L index scores

EQ-5D-5L	C3	C5	C7	C9	C11	C13	C15	C17	C19	C21	C23	C25	At DP
Utility index	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80	W88	W96	
Enco+Bini 450	[redacted]												
[redacted]													
[redacted]													
[redacted]													
p-value													

Abbreviations: C, cycle; CI, confidence interval; DCFB, difference in mean change from baseline; DP, disease progression; EQ-5D-5L, Euroqol-5 dimensions-5 levels; MCID, minimal clinically important difference; MMRM, mixed model repeated measures; W, Week.

** MCID reached (≥ 0.08 points for EQ-5D index score) between the Enco+Bini 450 and vemurafenib arms. Results versus Enco 300 were similar.*

Source: MMRM post-hoc analysis, data cut-off 19 May 2016, QoL post-hoc report [33]

Overall response rate (ORR)

The pivotal COLUMBUS trial also demonstrated that patients receiving Enco+Bini 450 treatment were more likely to achieve a clinically relevant reduction in tumour burden as defined by RECIST v1.1 compared to vemurafenib (ORR 63.5% vs. 40.8%) [11].

Duration of response (DOR)

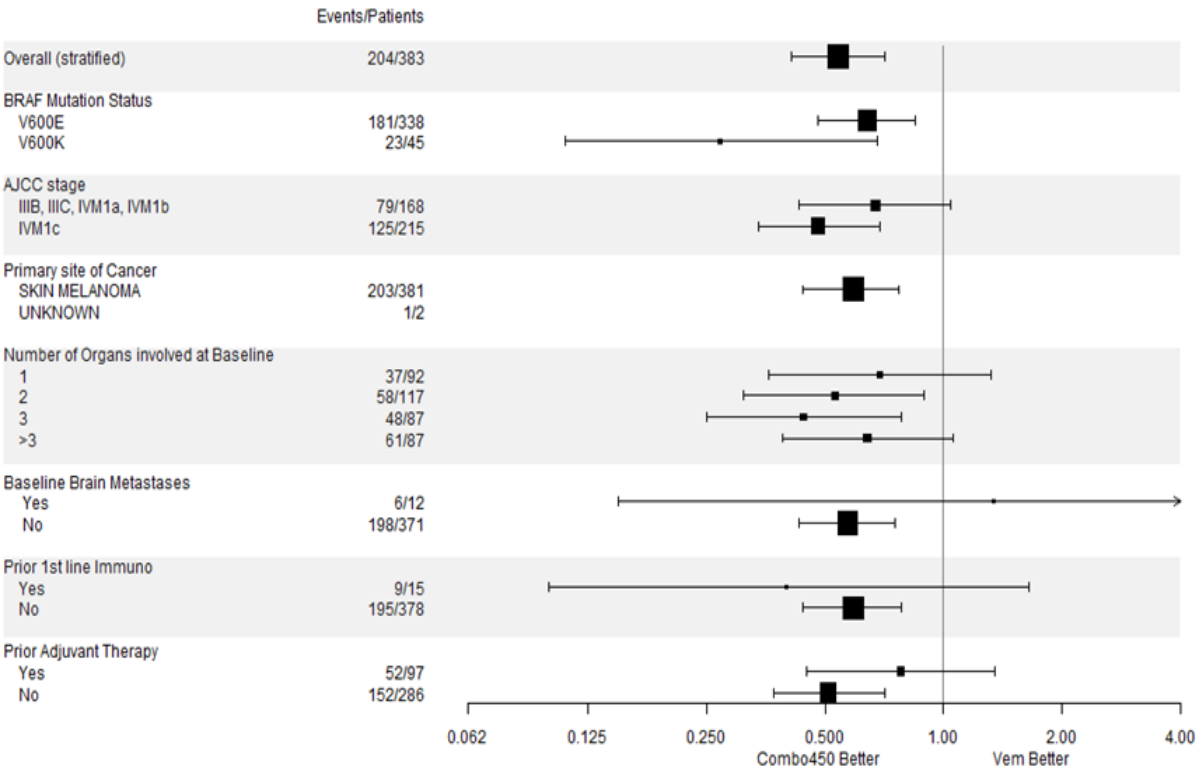
Responses on Enco+Bini 450 were meaningfully durable, lasting a median of 18.6 months compared to a DOR of 12.3 months for vemurafenib treatment [11].

Overall response rate (brain metastasis)

At baseline in COLUMBUS, nine patients in the Enco+Bini 450 arm (n=192) and three patients in the vemurafenib arm (n=191) had CNS involvement (brain metastasis) [28]. Subgroup analysis of PFS (BIRC) (Figure 8) illustrates the low number of patients with brain metastasis in the COLUMBUS trial. This number of patients did not permit generation of ORR data for this subgroup.

Similarly, for Dabra+Tram, the COMBI-v and COMBI-d trials specified brain metastases in the patient exclusion criteria and as such there are no data for this sub-group.

Figure 8: Forest plot of PFS based on BIRC for Enco+Bini 450 versus vemurafenib – FAS, Part 1, data cut-off 19 May 2016



Abbreviations: AJCC, American Joint Committee on Cancer; BIRC, Blinded Independent Review Committee; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CI, confidence interval; FAS, full analysis set; PFS, progression-free survival
Notes: the hazard ratio is obtained from an unstratified Cox model.
The CI was truncated for the subgroup of "yes" baseline brain metastases as it continued beyond the limits of the x-axis.
Source: CSR [28]*, Dummer et al 2018* [10].

5.3.2 COMBI-d

An overview of endpoints as per the Medicines Council's protocol is provided with the study characteristics in section 4.3.2.

The results of COMBI-d are presented in Table 11 and summarised below.

Table 11: Results of COMBI-d

Trial name:	COMBI-d							
NCT number:	NCT01584648							
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect	Estimated relative difference in effect			Description of methods used for estimation
				Difference	Hazard ratio	95% CI	P value	
OS Median, months	Dabra+Tram	211	25.1 (19.2–NE)	6.4 months	HR: 0.71	0.55–0.92	0.0107	The median survival is based on the KM estimator, using a Lan and DeMets α spending function, with O'Brien & Fleming-like boundaries to control the type 1 error rate. Source: Long et al. 2015 [18]
	Dabrafenib	212	18.7 (15.2–23.7)					
AEs – Patient with G≥3 events (%)	Dabra+Tram	209	48%	-2%%	NR			Adverse events were graded by the site investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) throughout the study until 30 days after the discontinuation of study treatment. Source: Long et al. 2017 [17]
	Dabrafenib	211	50%					
AEs – Patients with treatment discontinuation due to AE (%)	Dabra+Tram	209	11%	4%	NR			Source: Long et al. 2015 [18]
	Dabrafenib	211	7%					
PFS- per investigator Median, months	Dabra+Tram	211	11.0 months (8.0-13.9)	2.2 months	HR: 0.67	0.53–0.84	0.0004	The median survival is based on the KM estimator. The HR is based on a stratified log-rank test. Source: Long et al. 2015 [18]
	Dabrafenib	212	8.8 months (5.9-9.3)					
QLQ-C30 GH	Dabra+Tram	211		3.7- 5.8 point difference	NR			Analysis of covariance— adjusted for baseline score using mixed-model repeated

Trial name:	COMBI-d							
NCT number:	NCT01584648							
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect	Estimated relative difference in effect			Description of methods used for estimation
				Difference	Hazard ratio	95% CI	P value	
Change from baseline (week 8-40)	Dabrafenib	212						measures with time, treatment and treatment by time interaction as fixed effects—was carried out to assess differences between arms for global health and all functional and symptom dimension scores. Source: Schadendorf et al. 2015 [22]
ORR-per investigator	Dabra+Tram	211	68% (61.5–74.5)	13%	NR			Defined as the number of patients with a confirmed RECIST complete (CR) or partial response (PR) as a proportion of the total number of patients with measurable disease at baseline. Source: Long et al. 2017 [17]
	Dabrafenib	212	55% (47.8–61.5)					
ORR – brain metastasis	NR							NA
Duration of response Median, months	Dabra+Tram	144	12.0 (9.3–17.1)	1.4	NR			Defined as time from first RECIST response to progression. Source: Long et al. 2017 [17]
	Dabrafenib	116	10.6 (8.3–12.9)					

Abbreviations: AE(s): adverse event(s): BIRC: Blinded Independent Review Committee; CR: complete response; CI: confidence interval; DOR: duration of response; EORTC: European Organization for Research and Treatment of Cancer; FACT-M: Functional Assessment of Cancer Therapy; GH: Global Health; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; QLQ-C30: Core Quality of Life Questionnaire; NA: not applicable; NE: not estimated; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors

5.3.2.1. Summary of critical and important effect measures

Survival

3-year overall survival was 25.1 versus 18.7 months respectively, for Dabra+Tram versus monotherapy (HR: 0.71, 95%, CI: 0.55, 0.92; P = 0.0107) [18]. The 3- year overall survival was 44% and 32%, for Dabra+Tram versus monotherapy respectively [17].

Adverse events

With a median time on treatment of 11.8 (range, 0.4–43.7) versus 8.3 (range, 0.1–45.3) months in Dabra+Tram arm and dabrafenib arm patients, respectively, 49% versus 38% had >12 months of study treatment. AEs of any grade, regardless of study drug relationship, were observed in 97% of patients (both arms), with 48% of Dabra+Tram arm patients versus 50% of monotherapy patients experiencing ≥1 grade 3/4 adverse events and 45% versus 38% experiencing serious adverse events. The incidence of several AEs was higher (>10% difference, any grade) in the Dabra+Tram versus dabrafenib arm: pyrexia (59% versus 33%), chills (32% versus 17%), diarrhoea (31% versus 17%), vomiting (26% versus 15%), and peripheral oedema (22% vs 9%) [17]

Progression-free survival

Median PFS was longer in the Dabra+Tram arm (11.0 months) versus the dabrafenib monotherapy arm (8.8 months); (HR 0·67, 95% CI: 0·53, 0·84; P = 0·0004) [18]. At data cut-off, 3-year PFS was 22% for the Dabra+Tram arm and 12% for the dabrafenib monotherapy arm (HR: 0.71, 95%, CI: 0.57, 0.88) [17].

Health-related Quality of Life

Overall HRQoL as measured by the global health status score was statistically significantly better at weeks 8, 16 and 24 and clinically meaningful at week 40, for patients receiving Dabra+Tram compared with those receiving dabrafenib monotherapy during treatment (3.7- to 5.8-point difference) and at disease progression (3-point difference) [22].

Overall response rate

The confirmed ORR per RECIST was 68% for Dabra+Tram versus 55% for dabrafenib monotherapy, with complete response rates of 18% versus 15%, respectively [17].

Duration of response

Median DOR was 12.0 (95% CI, 9.3–17.1) for Dabra+Tram versus 10.6 (95% CI, 8.3–12.9) months for dabrafenib monotherapy [17].

5.3.3 COMBI-v

An overview of endpoints as per the Medicines Council's protocol is provided with the study characteristics in section 4.3.3.

The results of COMBI-v are presented in Table 12 and summarised below.

Table 12: Results of COMBI-v

Trial name:	COMBI-v									
NCT number:	NCT01597908									
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	P Value	Hazard ratio	95% CI	P value	
OS Median, months	Dabra+Tram	352	26.1 (NR)	NE	NR		HR: 0.68	0.56, 0.83	NR	The median survival is based on the KM estimator. The HR is based on a log rank test that was stratified for the BRAF mutation status (V600E vs. V600K) and the baseline level of LDH (>ULN). Source: SmPC Tafinlar, Mekinist (Updated OS analysis) [44,45]
	Vemurafenib	352	17.8 (NR)							
AEs – Patient with G3-4 events	Dabra+Tram	350	52%	-11%	NR		NR			Adverse events were graded by the site investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) The safety analysis included the 699 patients who received at least one dose of a study drug Source: Robert et al. 2015 [14]
	Vemurafenib	349	63%							
AEs – Patients with treatment discontinuation due to AE	Dabra+Tram	350	13%	1%	NR		NR			
	Vemurafenib	349	12%							
PFS Median, months	Dabra+Tram	352	11.4	4.1	NR		HR: 0.56	0.46, 0.69	<0.001	The median survival is based on the KM estimator. The HR is based on a log rank test that was stratified for the BRAF mutation status (V600E vs. V600K) and the baseline level of LDH (>ULN). Source: Robert et al. 2015 [14]
	Vemurafenib	352	7.3							
FACT-M Change from baseline (week 48)	Dabra+Tram	139	1.98	3.00	1.52–4.48	<0.001	NR			Changes of the mean scores were analysed over time with a repeated measures ANCOVA by use of baseline score as covariate with time, treatment, baseline score, baseline score by time interaction, and treatment by time interaction as fixed effects p values are based on the two-sided Wald test.
	Vemurafenib	85	-1.02							
QLQ-C30 GH	Dabra+Tram	148	3.00	7.56	3.56–11.57	<0.001	NR			

Trial name:	COMBI-v									
NCT number:	NCT01597908									
Outcome	Study arm	N	Result (95% CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	P Value	Hazard ratio	95% CI	P value	
Change from baseline (week 48)	Vemurafenib	86	-4.57							Source: Grob et al. 2015 [24]
ORR % (95% CI)	Dabra+Tram	351	67.0% (62,72)	14%			NR			Included in the objective response are complete and partial responses. Source: Robert et al. 2016 [15]
	Vemurafenib	350	53% (48,59)							
ORR – brain metastasis	NR									
Duration of response Median, months (95% CI)	Dabra+Tram	351	13.8 (11.3,17.6)	6.2 months	NR		NR			Source: Robert et al. 2016 [15]
	Vemurafenib	350	7.6 (7.4,9.3)							

Abbreviations: AE(s): adverse event(s): BIRC: Blinded Independent Review Committee; CR: complete response; CI: confidence interval; DOR: duration of response; FACT-M: Functional Assessment of Cancer Therapy: GH: Global Health; HR: hazard ratio; KM: Kaplan-Meier; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; QLQ-C30: Core Quality of Life Questionnaire; NE, not estimable; NR: not reported; PR: partial response; ULN: upper limit of normal

5.3.3.1. Summary of critical and important effect measures

Survival

The median 3 year overall survival was 26.1 months for Dabra+Tram versus 17.8 months (HR=0.68, 95% CI 0.56, 0.83) for vemurafenib [44,45].

Adverse events

The safety analysis included the 699 patients who received at least one dose of a study drug. Most patients had AEs that were deemed by the investigator to be related to the study treatment: 91% in the Dabra+Tram group and 98% in the vemurafenib group. The rates of permanent treatment discontinuation because of AEs were similar (13% and 12%, respectively). The most common reasons for discontinuation were pyrexia and decreased ejection fraction (3% for each event) in the Dabra+Tram group and arthralgia (2%) in the vemurafenib group. The most frequent AEs in the Dabra+Tram group were pyrexia (53%), nausea (35%), diarrhoea (32%), chills (31%), fatigue (29%), headache (29%), and vomiting (29%). In the vemurafenib group, the most frequent AEs were arthralgia (51%), rash (43%), alopecia (39%), diarrhoea (38%), nausea (36%), and fatigue (33%). Grade 3 or 4 AEs occurred in 52% of the patients in the combination therapy group and in 63% of those in the vemurafenib group [14].

Progression-free survival

Median PFS was longer in the Dabra+Tram group than in the vemurafenib group (11.4 months vs. 7.3 months; HR 0.56; 95% CI, 0.46 to 0.69; P<0.001) [14].

Health-related quality of life

Mean baseline EQ-5D utility scores were similar between treatment groups (0·751 for combination therapy vs 0·715 for vemurafenib). Among patients receiving Dabra+Tram, health utility mean scores increased (i.e. improved) relative to baseline scores for all follow-up assessments, including at disease progression. For patients receiving vemurafenib, these scores increased or were unchanged at weeks 8, 16, and 24, but slightly decreased at weeks 32, 40, and 48, and at disease progression. When assessed for differences between treatment groups with mixed-model repeated measures analyses, health utility scores were significantly better (p<0.05) and clinically meaningful (0.08–0.11 for the health utility score) for the combination than for vemurafenib for all assessments (Table 13).

Overall response rate

The ORR was 67% (95% CI: 62, 72) in the Dabra+Tram group versus 53% (95% CI: 48, 59) in the vemurafenib group [15].

Duration of response

The median DOR was 13.8 months (95% CI: 11.3, 17.6) and 7.6 months (95% CI: 7.4, 9.3), respectively [15].

5.3.4 Results per study overview

Both the critical and important outcomes for each study are presented in Table 13.

Table 13: Summary of results per study

Outcome measure		COLUMBUS (Enco+Bini 450 vs vemurafenib)	COMBI-v (Dabra+Tram vs vemurafenib)	COMBI-d (Dabra+Tram vs dabrafenib)
Critical	**Overall survival** Median, months HR (95% CI)	33.6 vs. 16.9 months [11] 0.61 (0.47-0.79) P<0.001	26.1 vs. 17.8 months [44,45] 0.68 (0.56-0.83) P= NR	25.1 vs. 18.7 months [18] 0.71 (0.55-0.92) P=0.0107
	AEs – Patients with grade 3-4 events	57.8% vs. 63.4% [10]†	52.0% vs. 63.0% [14]	48.0% vs. 50.0% [17]
	AEs – Patients with treatment discontinuation due to AEs	12.5% vs. 16.7% [10] †	13.0% vs. 12.0% [14]	11.0% vs. 7.0% [18]
Important	**Progression-free survival* (per investigator)** Median, months HR (CI 95%), p-value	14.9 vs. 7.3 [11] 0.51 (0.39-0.67), P<0.0001	11.4 vs. 7.3 [14] 0.56 (0.46 to 0.69), P<0.001	11.0 vs. 8.8 [18] 0.67 (0.53-0.84), P=0.0004
	EQ-5D utility score- DCFB at week 16	[redacted]	+0.09 [23] P<0.001	NR
	EQ-5D utility score- DCFB at week 48	[redacted]	+0.11 [23] P<0.001	NR
	EQ-5D utility score- DCFB at disease progression	[redacted]	+0.11 [23] P<0.001	NR
	ORR % (95% CI)	63.5% (56.3-70.4) vs. 40.8% (43.8-48.2) [11]	67% (62-72) vs. 53% (48-59) [15]	68% (61.5-74.5) vs. 55% (47.8-61.5) [17]
	Duration of response Median, months (95% CI)	18.6 (12.7-24.1) vs. 12.3 (6.9-14.5) [11]	13.8 (11.3-17.6) vs 7.6 (7.4-9.3) [15]	12.0 (9.3-17.1) vs 10.6 (8.3-12.9) [17]

Abbreviations: AE(s): adverse event(s); BIRC, blinded independent review committee; CI: confidence interval; EQ-5D: Euroqol-5 dimensions questionnaire; HR: hazard ratio; NR, not reported; ORR, overall response rate

†COLUMBUS (Part 1) safety set; Enco+Bini 450 (n=192), vemurafenib (n=186)

** Progression-free survival assessed by BIRC is presented for the COLUMBUS trial whereas this was investigator-assessed in the Combi-v and Combi-d trials.*

A naïve, side-by-side comparison of the outcomes for Enco+Bini 450 versus vemurafenib (COLUMBUS) and Dabra+Tram versus vemurafenib (COMBI-v) is also presented. These two studies were selected as they are both direct comparisons of the respective treatments versus vemurafenib, which enables naïve comparisons of their outcomes provided that they show comparability in terms of patient and study characteristics. However, the major limitation of this type of comparison, as noted by Bucher *et al.* [46], is that naïve direct comparisons of results across different trials 'break' the original randomisation and are subject to significant confounding and bias because of systematic differences between or among the trials being compared [47].

Assessment of effect modification: baseline patient and study characteristics of COLUMBUS and COMBI-v

Baseline patient characteristics in both COLUMBUS and COMBI-v trials were comparable (intention to treat populations). In COLUMBUS, the median age for Enco+Bini 450 and vemurafenib was 57 and 56 years respectively [11], the median age in COMBI-v was 55 years for both Dabra+Tram and vemurafenib arms [14]. 89% and 88% of patients enrolled in COLUMBUS had a BRAFV600E mutation at baseline in the Enco+Bini 450 and vemurafenib arms respectively. This is comparable to COMBI-v, where 90% of patients in both the Dabra+Tram and vemurafenib arms had a BRAFV600E mutation at baseline. The majority of patients in both COLUMBUS (64% in the Enco+Bini 450 arm versus 65% in the vemurafenib arm) and COMBI-v (63% in the Dabra+Tram arm versus 61% in the vemurafenib arm) were classified as American Joint Committee on Cancer (AJCC) tumour stage IVM1c at study entry. Furthermore, the overall survival and PFS results for the vemurafenib are were similar in both COLUMBUS and Combo-v trials (overall survival: 16.9 and 17.8 months, respectively; PFS: 7.3 months in both), suggesting comparability of patient populations.

With regards to study design, both COLUMBUS and COMBI-v were found to be comparable in terms of study design, randomisation, patient inclusion criteria and prior therapy [11,14] . Of note, both trials had an open-label design, a design which increases the risk of bias, in particular when it comes to HRQoL outcomes. COLUMBUS used blinded independent review committee (BIRC) to assess the PFS, in order to minimise bias from the open label design, whereas COMBI-v used per-investigator assessment.

Naïve comparison of outcomes from COLUMBUS and COMBI-v

A naïve comparison between COLUMBUS and COMBI-v is provided in Table 14 and outlined below:

- *Overall survival:* Enco+Bini 450 versus vemurafenib demonstrated an improvement in median overall survival of 16.7 months (33.6 versus 16.9 months), whereas an improvement of 8.3 months was achieved with Dabra+Tram versus vemurafenib (26.1 versus 17.8 months). The difference between Enco+Bini 450 and Dabra+Tram in absolute improvement on median overall survival versus vemurafenib (8.4 months), exceeds the minimum clinically relevant difference of 3 months, as specified by the Medicine Council's protocol.

- *AEs (grade 3–4):* Patients in the Enco+Bini 450 arm of COLUMBUS experienced fewer grade 3–4 AEs compared to the vemurafenib arm (57.8% versus 63.4%, respectively); 52% of Dabra+Tram patients experienced grade 3–4 AEs compared to 63% of patients in the vemurafenib arm. The difference between Enco+Bini 450 and Dabra+Tram versus vemurafenib, is less than the minimum clinically relevant difference of 10% points for grade 3–4 AEs, as specified by the Medicine Council's protocol.
- *Treatment discontinuation due to AEs:* Enco+Bini 450 had a lower proportion of patients discontinuing due to AEs, compared to vemurafenib (12.5% versus 16.7%); whereas Dabra+Tram had a higher rate of patients discontinuing due to AEs compared to vemurafenib (13.0% versus 12.0%). The absolute difference between Enco+Bini 450 and Dabra+Tram, exceeds the minimum clinically relevant difference of 5% points as specified by the Medicine Council's protocol.
- *Progression-free survival:* Enco+Bini 450 demonstrated an improvement in median PFS of 7.6 months versus vemurafenib (14.9 versus 7.3 months); Dabra+Tram demonstrated an improvement of 4.1 months versus vemurafenib (11.4 versus 7.3 months). The difference in improvement versus vemurafenib between Enco+Bini 450 and Dabra+Tram is 3.5 months, which exceeds the minimum clinically relevant difference in median PFS of 3 months, as specified by the Medicine Council's protocol.
- *Health-related quality of life:* The difference in EQ-5D-5L index score was numerically in favour of the Enco+Bini 450 arm versus vemurafenib, although the minimal clinically important difference (≥0.08 points) [43] was only reached at the last visit at week 16. (P <0.0001*)*. Similarly, mean utility scores reached the MCID for Dabra+Tram at week 8 and 16, meeting the minimum clinically important difference specified by the Medicine Council's protocol, and indicating comparability between both treatments.
- *Overall response rate:* The ORR for Enco+Bini 450 versus vemurafenib were 63.5% and 40.8% respectively; ORR rates for Dabra+Tram versus vemurafenib were 67% and 53% respectively. The difference in the absolute improvement of the ORR between Enco+Bini 450 and Dabra+Tram is 8.7%, which is close to the Medicine Council's minimum clinically relevant difference of 10%.
- *ORR – brain metastasis*: Data are not available for this outcome; thus, a comparison was not possible (see section 5.4.1.1).
- *Duration of response:* Enco+Bini 450 achieved a more prolonged median DOR in comparison to vemurafenib of 6.3 months (median DOR of 18.6 versus 12.3 months. respectively). Dabra+Tram demonstrated a prolonged median DOR in comparison to vemurafenib monotherapy of 6.2 months (median DOR of 13.8 versus 7.6 months respectively). The difference in absolute

improvement in median DOR between Enco+Bini 450 and Dabra+Tram in this naïve comparison is less than the Medicine Council's minimum clinically relevant difference of 2 months.

Table 14: Naive comparison COLUMBUS and COMBI-v outcomes

Outcome measure		Study outcomes		Absolute difference in effect
		COLUMBUS (Enco+Bini 450 vs vemurafenib)	**COMBI-v** (Dabra+Tram vs vemurafenib)	
Critical	**Overall survival** Median, months HR (95% CI)	33.6 vs. 16.9 months [11] 0.61 (0.47-0.79) P<0.001	26.1 vs. 17.8 months [15,48] 0.68 (0.56-0.83) P=NR	8.4 months
	AEs – Patients with grade 3-4 events	57.8% vs. 63.4% [10]†	52.0% vs. 63.0% [14]	5.4%
	AEs – Patients with treatment discontinuation due to AEs	12.5% vs. 16.7% [10] †	13.0% vs. 12.0% [14]	-5.2%
Important	**Progression-free survival* (per investigator)** Median, months HR (CI 95%), p-value	14.9 vs. 7.3 [11] 0.51 (0.39-0.67), P<0.0001	11.4 vs. 7.3 [14] 0.56 (0.46 to 0.69), P<0.001	3.5 months
	EQ-5D utility score- DCFB at week 16	[redacted]	+0.09 [23] P<0.001	[redacted]
	EQ-5D utility score- DCFB at week 48	[redacted]	+0.11 [23] P<0.001	[redacted]
	EQ-5D utility score- DCFB at disease progression	[redacted]	+0.11 [23] P<0.001	[redacted]
	ORR % (95% CI)	63.5% (56.3-70.4) vs. 40.8% (43.8-48.2) [11]	67% (62-72) vs. 53% (48-59) [15]	8.7%
	Duration of response Median, months (95% CI)	18.6 (12.7-24.1) vs. 12.3 (6.9-14.5) [11]	13.8 (11.3-17.6) vs 7.6 (7.4-9.3) [15]	0.1 months

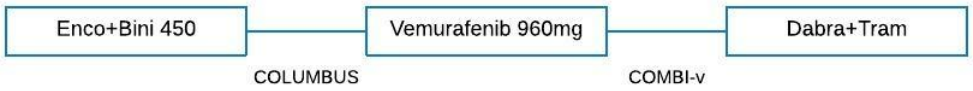
Abbreviations: AE(s): adverse event(s); BIRC, blinded independent review committee; CI: confidence interval; EQ-5D: Euroqol-5 dimensions questionnaire; HR: hazard ratio; ORR, overall response rate

*†COLUMBUS (Part 1) safety set; Enco+Bini 450 (n=192), vemurafenib (n=186), * Progression-free survival assessed by BIRC is presented for the COLUMBUS trial whereas this was investigator-assessed in the Combi-v trial.*

5.4 Comparative analyses

In light of the limitations of naïve comparisons and in the absence of head-to-head evidence comparing the efficacy and safety of Enco+Bini 450 with Dabra+Tram for the management of unresectable or metastatic BRAF V600 mutation-positive melanoma, an indirect treatment comparison (ITC) was conducted using the Bucher method [49]. For each outcome, ITC was performed comparing Enco+Bini 450 with Dabra+Tram via the common comparator, vemurafenib, used in the COLUMBUS and COMBI-v trials (Figure 9, Table 15).

Figure 9: ITC network of evidence



Abbreviations: Dabra+Tram, dabrafenib in combinatino wtih trametinib; Enco+Bini 450, encorafenib in combination with binimetinib

Given the use of fixed-effects models, statistical tests for heterogeneity were not appropriate. However, assessment of effect modification and risk of bias, indicated that no substantial inconsistency was detected in between the COLUMBUS or COMBI-v trials. This was expected because, as highlighted in section 4.3 and section 5.2, the studies had similar study design and patient characteristics. Further information on the assessment of effect modification and risk of bias between COLUMBUS and COMBI-v is provided in Appendix C, section C.1. A description of the method used for evidence synthesis and a summary of the input data, are provided in Appendix C, section C.2.

An overview of the results of the ITC are presented in Table 15. Enco+Bini 450 was numerically better than Dabra+Tram for OS, PFS, discontinuation due to AEs and any serious AEs. The ORR for Enco+Bini 450 versus Dabra+Tram was numerically in favour of Enco+Bini 450, results of which were statistically significant. Dabra+Tram was associated with numerically lower rates of any grade ≥3 AEs. With the exception of the ORR, results were not statistically significant.

Of note, indirect comparisons were conducted for estimates of odds ratio (OR), rather than relative risk (RR), as the indicator of relative treatment effect for the safety outcomes and ORR. Conducting indirect comparisons on RRs can give inferential fallacies whereas ORs always give correct, consistent results [50]. ORs are very close to RRs when the probability of an event is very small and there are methods for converting between OR and RR. The method by Zhang is a simple method of converting OR to RR, which relies on the assumption of the control group risk, commonly the mean or median of the control group risk in the studies that have been used in the meta-analysis [51]. However, this method is not accurate and has been criticised, and it is recommended that an attempt to convert between OR and RR is not pursued.

Table 15: ITC results

Outcome	Enco+Bini 450 vs. Dabra+Tram
OS, HR (95% CI)†	0.90 (0.65, 1.24)
Any grade 3–4 AEs, OR (95% CI)§	1.07 (0.64, 1.80)
Discontinuation due to AEs, OR (95% CI)§	0.67 (0.33, 1.36)
Any serious AEs, OR (95% CI)§	0.80 (0.47, 1.34)
PFS (per investigator), HR (95% CI)†	0.80 (0.58, 1.11)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ORR (per investigator), OR (95% CI)‡	1.77 (1.04, 3.02)
DOR (per investigator), Median difference, months (95% CI)	2.6 (-5.15, 10.35)

Abbreviations: AE(s), adverse event(s); CI, confidence interval; DCFB, difference in change from baseline; DOR, duration of response; EQ-5D, Euroqol-5 dimensions questionnaire; HR, hazard ratio; ITC, indirect treatment comparison; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

† HR<1 suggests a favourable result for Enco+Bini 450; ‡ OR>1 suggests a favourable result for Enco+Bini 450; § OR<1 suggests a favourable result for Enco+Bini 450.

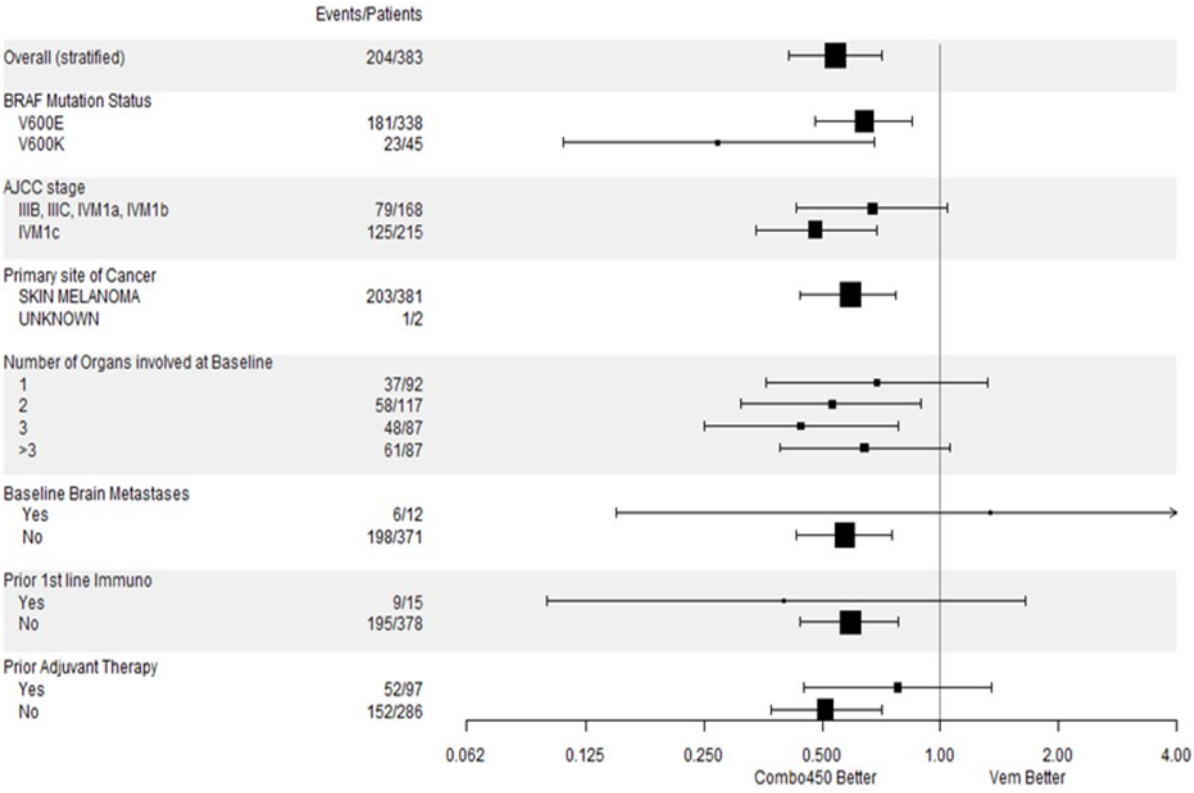
Notes: All efficacy outcomes for COLUMBUS based on November 2017 data cut-off, with the expection of PFS which is based on published PFS (per investigator) from the May 2016 data-cut; all safety outcomes for COLUMBUS based on May 2016 data cut-off; all HRQoL outcomes for COLUMBUS based on May 2016 data cut off

5.4.1.1. Central nervous system (CNS) metastasis overall response rate

At baseline in COLUMBUS, [redacted] patients in the Enco+Bini 450 arm (n=192) and [redacted] patients in the vemurafenib arm (n=191) had CNS involvement (brain metastasis) [28]. Subgroup analysis of PFS (BIRC) (Figure 10) illustrates the low number of patients with brain metastasis in the COLUMBUS trial. This number of patients did not permit generation of ORR data for this subgroup.

Similarly, for Dabra+Tram, the COMBI-v and COMBI-d trials specified brain metastases in the patient exclusion criteria and as such there are no data for this sub-group.

Figure 10: Forest plot of PFS based on BIRC for Enco+Bini 450 versus vemurafenib – FAS, Part 1, data cut-off 19 May 2016



Abbreviations: AJCC, American Joint Committee on Cancer; BIRC, Blinded Independent Review Committee; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; PFS, progression-free survival

The CI was truncated for the subgroups of "yes" baseline brain metastases, Australia and "yes" Japanese as they continued beyond the limits of the x-axis.

Notes: Figure depicts patients with prior immunotherapy in both adjuvant and metastatic settings.

The hazard ratio is obtained from an unstratified Cox model.

Source: CSR [28]*, Dummer et al 2018* [10].

5.4.2 Summary of relative treatment efficacy, safety and HRQoL

Direct comparative evidence is not available for Enco+Bini 450 versus Dabra+Tram. An ITC was conducted to elicit estimates of relative treatment efficacy, safety and HRQoL for these two treatments.

The ITC shows a numerical advantage of Enco+Bini 450 versus Dabra+Tram with respect to OS, PFS and discontinuation due to AEs (Table 16). The ITC results should be interpreted with caution, given that the 95% confidence intervals crossed the line of equal effect. Nevertheless, they supplement the findings of the naïve comparison, which showed a clinically relevant difference in favour of Enco+Bini 450 compared with Dabra+Tram in terms of absolute improvement in median overall survival and PFS versus vemurafenib.

Table 16: Results pertaining to the Clinical question

Outcome measure		Studies included in the analysis	Absolute difference in effect [from the Naïve comparison]		Relative difference in effect [from the ITC]		Methods used for quantitative synthesis
			Difference	CI (95%)	Hazard/Odds ratio	CI (95%)	
Critical	**Overall survival**	COLUMBUS, COMBI-v	8.4 months	NA	HR: 0.90†	0.65, 1.24	Analysed using log transformed HR and corresponding standard errors (SE), assuming a normal distribution followed by a Bucher method analyses as described by Bucher et al 1997 [46]
	AEs – Patient with G3-4 events		5.4%	NA	OR: 1.07§	0.64, 1.80	Analysed as binary outcomes, assuming a binomial likelihood distribution, followed by a Bucher method analyses as described by Bucher et al 1997 [46]
	AEs – Patients with treatment discontinuation due to AEs		-5.2%	NA	OR: 0.67§	0.33, 1.36	
Important	**Progression-free survival (per investigator)**		3.5 months	NA	HR: 0.80†	0.58, 1.11	Analysed using log transformed HR and corresponding standard errors (SE), assuming a normal distribution, followed by a Bucher method analyses as described by Bucher et al 1997 [46]
	EQ-5D utility score, pre-progression *		-0.010	NA	-0.02	-0.05,0.01	Analysed as continuous outcomes applying a normal distribution and identity link.
	EQ-5D utility score, DCFB at week 32 *		-0.045	NA	-0.04	-0.10, 0.02	
	EQ-5D utility score, DCFB at disease progression *		-0.040	NA	-0.04	-0.12, 0.04	
	ORR (per-investigator)		8.7%	NA	OR: 1.77‡	1.04, 3.02	Analysed as binary outcomes, assuming a binomial likelihood distribution, followed by a Bucher method analyses as described by Bucher et al 1997 [46]
	ORR – brain metastasis		NR		NR		NA
	Duration of response (per investigator)		0.1 months	NA	2.6	-5.15, 10.35	Analysed as binary outcomes, assuming a binomial likelihood distribution, followed by a Bucher method analyses as described by Bucher et al 1997 [46]

Abbreviations: AE(s): adverse event(s); CI: confidence interval; EQ-5D: Euroqol-5 dimensions questionnaire; HR: hazard ratio; NA, not-applicable; NR, not reported; ORR, overall response rate
**COLUMBUS and COMBI-v only. † HR<1 suggests a favourable result for Enco+Bini 450; ‡ OR>1 suggests a favourable result for Enco+Bini 450; § OR<1 suggests a favourable result for Enco+Bini 450*

5.5 Interpretation and conclusions of the evidence

Enco+Bini 450 is a BRAFi/ MEKi combination therapy that has demonstrated both clinical and HRQoL benefits in patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The pivotal Phase 3 trial (COLUMBUS) demonstrated clinically meaningful improvements in key efficacy endpoints over the existing licensed BRAFi monotherapy, vemurafenib, approximately doubling both overall survival and PFS, and leading to a clinically relevant and durable reduction in tumour burden and delaying deterioration in HRQoL. The absolute median overall survival of 33.6 months achieved with Enco+Bini 450 treatment in the COLUMBUS trial, represents the longest overall survival reported of any BRAFi/ MEKi (Dabra+Tram median overall survival: COMBI-v = 26.1 months; COMB-d = 25.1 months). In a naïve comparison, the absolute improvement for Enco+Bini 450 compared with Dabra+Tram on median overall survival and PFS versus vemurafenib was 8.4 months greater for overall survival and 3.5 months greater for PFS; these differences exceed the minimal clinically important threshold of 3 months. Additionally, ITC of Enco+Bini 450 with Dabra+Tram showed numerical improvements in overall survival and PFS (overall survival: HR 0.90; 95% confidence interval: 0.65, 1.24; PFS (per investigator): HR 0.77; 95% confidence interval: 0.56, 1.06). As such, Enco+Bini 450 represents an advancement in the management of unresectable or metastatic BRAF V600 mutation-positive melanoma.

Characteristic toxicities associated with BRAFi/ MEKi combination therapies were generally manageable, reversible, and infrequently associated with treatment discontinuation with Enco+Bini 450, and showed a differential tolerability and toxicity profile to the combination of Dabra+Tram. The demonstrated benefits of Enco+Bini 450, support its choice as a preferred treatment for many patients.

6. References

[1] Laboratoires Pierre Fabre. Summary of Product Characteristics: Encorafenib 2017.
[2] Delord J-P, Robert C, Nyakas M, McArthur GA, Kudchakar R, Mahipal A, et al. Phase I Dose-Escalation and -Expansion Study of the BRAF Inhibitor Encorafenib (LGX818) in Metastatic BRAF-Mutant Melanoma. Clin Cancer Res 2017;23:5339–48. doi:10.1158/1078-0432.CCR-16-2923.
[3] Stuart DD, Li N, Poon DJ, Aardalen K, Kaufman S, Merritt H, et al. Abstract 3790: Preclinical profile of LGX818: A potent and selective RAF kinase inhibitor. Cancer Res 2012;72:3790–3790. doi:10.1158/1538-7445.AM2012-3790.
[4] Laboratoires Pierre Fabre. Summary of Product Characteristics: Binimetinib 2017.
[5] Bendell JC, Javle M, Bekaii-Saab TS, Finn RS, Wainberg ZA, Laheru DA, et al. A phase 1 dose-escalation and expansion study of binimetinib (MEK162), a potent and selective oral MEK1/2 inhibitor. Br J Cancer 2017;116:575–83. doi:10.1038/bjc.2017.10.
[6] WebMD. What is the most serious form of skin cancer? 2018. https://www.webmd.com/melanoma-skin-cancer/qa/what-is-the-most-serious-form-of-skin-cancer.
[7] Dansk Melanom Database. National Årsrapport 2017 2018.
[8] RADS. Behandlingsvejledning for metastaserende malignt melanom 2016.
[9] Dansk Melanom Gruppe. Danish Metastatic Melanoma Database. 2017.
[10] Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018;0. doi:10.1016/S1470-2045(18)30142-6.
[11] Dummer R, Ascierto PA, Gogas H, Arance AM, Mandalà M, Liszkay G, et al. Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma. J Clin Oncol 2018;36:9504–9504. doi:10.1200/JCO.2018.36.15_suppl.9504.
[12] NICE. The guidelines manual | Guidance and guidelines 2012.
[13] Gogas H, Dummer R, Ascierto PA, Arance AM, Mandalà M, Liszkay G, et al. Adverse events of special interest in the phase 3 COLUMBUS study. J Clin Oncol 2018;36:9504.
[14] Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30–9. doi:10.1056/NEJMoa1412690.
[15] Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroyakovskiy D, et al. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. Ann Oncol 2016;27. doi:10.1093/annonc/mdw435.37.
[16] Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371:1877–88. doi:10.1056/NEJMoa1406037.
[17] Long GV, Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol Off J Eur Soc Med Oncol 2017;28:1631–9. doi:10.1093/annonc/mdx176.
[18] Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. The Lancet 2015;386:444–51. doi:10.1016/S0140-6736(15)60898-4.
[19] Gogas H, Dummer R, Ascierto PA, Mandala M, Liszkay G, Garbe C, et al. Quality-of-Life (QoL) in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant Melanoma. Ann Oncol 2017;28 (Suppl_5):v428–48.
[20] Robert C, Schadendorf D, Long GV, Stroyakovskiy D, Levchenko E, Chiarion-Sileni V, et al. Analysis of patient-reported outcomes by disease progression status in patients (pts) with BRAF V600-mutant metastatic melanoma in the COMBI-d and COMBI-v trials. Ann Oncol Conf 41st Eur Soc Med Oncol Congr ESMO 2016;27.

[21] Grob JJ, Robert C, Long GV, Stroyakovskiy D, Levchenko E, Chiarion-Sileni V, et al. Health-related quality-of-life (HRQOL) impact of dabrafenib (D) and trametinib (T) vs BRAF inhibitor (BRAFi) monotherapy by lactate dehydrogenase (LDH) in patients (pts) with BRAF V600-mutant melanoma. Ann Oncol Conf 41st Eur Soc Med Oncol Congr ESMO 2016;27.
[22] Schadendorf D, Amonkar MM, Stroyakovskiy D, Levchenko E, Gogas H, de Braud F, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. Eur J Cancer 2015;51:833–40.
[23] Grob JJ, Amonkar MM, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol 2015;16:1389–98.
[24] Grob JJ, Amonkar M, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. COMBI-v: Health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with BRAF V600 metastatic melanoma (MM). Eur J Cancer 2015;51:S682–3.
[25] Dummer R, Ascierto PA, Gogas H, Arance A, Mandalà M, Liszkay G, et al. Results of COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant Melanoma 2016.
[26] Arance A, Dummer R, Ascierto P, Gogas H, Mandala M, Liszkay G, et al. Hospitalization Rates in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib Plus Binimetinib vs Vemurafenib or Encorafenib Monotherapy in BRAF-Mutant Melanoma. Ann Oncol 2017;28 (Suppl_5):v428–48.
[27] Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018;19:1315–27. doi:10.1016/S1470-2045(18)30497-2.
[28] Array BioPharma Inc. A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma: Clinical Study CMEK162B2301. 2017.
[29] Laboratoires Pierre Fabre. Summary of clinical safety, Section 2.7.4., 4-month update. 9 November 2016 data cut-off. 2018.
[30] Array BioPharma Inc. COLUMBUS clinical study report: Analysis of Overall Survival at November 2017 Data cut. 2018.
[31] Array BioPharma Inc. Part 1 OS Topline Results. COLUMBUS: A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma. 2018.
[32] Array BioPharma Inc. Efficacy update CMEK162B2301: 7 November 2017 data cut-off. 2018.
[33] Laboratoires Pierre Fabre. COLUMBUS: Post-hoc QoL analyses report [commercial in confidence]. 2018.
[34] Laboratoires Pierre Fabre. Data on file. Post-hoc analyses of COLUMBUS phase III trial: Part II Efficacy and Safety Endpoints with Encorafenib in Combination with Binimetinib in Unresectable or Metastatic Melanoma for BRAF-mutated Patients. 2018.
[35] Dummer R, Hauschild A, Guggenheim M, Keilholz U, Pentheroudakis G. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23:vii86–91.
[36] National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) v4.03 2010.
[37] European Medicines Agency. Mektovi. European Public Assessment Report (EPAR). Committee for Medicinal Products for Human Use (CHMP); 2018.
[38] European Medicines Agency (EMA). Braftovi. European Public Assessment Report (EPAR). 26/07/2018; n.d.
[39] Dréno B, Ribas A, Larkin J, Ascierto PA, Hauschild A, Thomas L, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. Ann Oncol Off J Eur Soc Med Oncol 2017;28:1137–44. doi:10.1093/annonc/mdx040.

[40] IQVIA,. KOL VALIDATION: Economic evaluation of EncoBini in patients with unresectable or metastatic BRAFV600 mutant melanoma: Denmark 2018.
[41] Askew RL, Xing Y, Palmer JL, Cella D, Moye LA, Cormier JN. Evaluating minimal important differences for the FACT-Melanoma quality of life questionnaire. Value Health J Int Soc Pharmacoeconomics Outcomes Res 2009;12:1144–50. doi:10.1111/j.1524-4733.2009.00570.x.
[42] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol Off J Am Soc Clin Oncol 1998;16:139–44. doi:10.1200/JCO.1998.16.1.139.
[43] Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:70. doi:10.1186/1477-7525-5-70.
[44] Novartis Europharm Ltd. Summary of product characteristics: Dabrafenib (Tafinlar) 50mg and 75mg capsules. 2017.
[45] Novartis Europharm Ltd. Summary of product characteristics: Trametinib (Mekinist) 0.5mg and 2mg tablets. 2017.
[46] Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683–91.
[47] Kim H, Gurrin L, Ademi Z, Liew D. Overview of methods for comparing the efficacies of drugs in the absence of head-to-head clinical trial data. Br J Clin Pharmacol 2014;77:116–21. doi:10.1111/bcp.12150.
[48] Robert,Caroline. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. ESMO, Copenhagen 2016.
[49] Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683–91.
[50] Eckermann S, Coory M, Willan AR. Indirect comparison: relative risk fallacies and odds solution. J Clin Epidemiol 2009;62:1031–6. doi:10.1016/j.jclinepi.2008.10.013.
[51] Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690–1.

Assessment of the clinical added value of BRAFTOVI® in combination with MEKTOVI® in unresectable or metastatic melanoma for BRAF-mutated patients

Appendices to the application to the Medicine Council

October 2018

Contents

Purpose of the document

This document contains the appendices to the application to the Medicine Council for the assessment of the clinical added value of BRAFTOVI® in combination with MEKTOVI® in unresectable or metastatic melanoma for BRAF-mutated patients.

Appendix A. Clinical literature search

A.1 Scope of the review

The PICOS statement for the clinical SLR is outlined in Table A. 1 below.

Table A. 1: PICOS statement for clinical SLR

Criteria	Definition
Patient population	Adult (18 years and older) patients with unresectable or metastatic cutaneous melanoma
Intervention	Encorafenib (combined with) binimetinib, dabrafenib, vemurafenib, trametinib, cobimetinib, ipilimumab, nivolumab, pembrolizumab (lambrolizumab), atezolizumab, talimogene, dacarbazine, temozolomide, fotemustine, vindesine, interferon, interleukin-2, taxanes, platinum derivatives (monotherapy or combination therapy (2 drugs or more))
Comparators	Any treatment from the above mentioned list of interventions (monotherapy or combination therapy (2 drugs or more)) OR Placebo or best supportive care
Outcomes measures	**Efficacy** PFS, OS, ORR, CR, PR, TTR, DOR, DCR, BOR, SD, PD **Safety** Rates of treatment related AEs, recurrence rates after treatment, treatment discontinuation due to AE, dose report, dose reduction, grade 3/4, serious AE, dose intensity, dose exposure, type of AE, hospitalisation rate (reason for hospitalisation and duration)
Study design	RCTs OR Observational studies OR (All studies must include at least 10 patients and 10 patients per comparator arm for RCTs)

Abbreviations: AE: adverse event; BOR: best overall response; CR: complete response; DCR: disease control rate; DOR: duration of response; ORR: objective/overall response rate; OS: overall survival; PD: progressed disease; PFS: progression free survival; PR: partial response; RCT: randomised controlled trial; SD: stable disease; TTR: time to response

A.2 Databases used in searches

The databases used in the searches are outlined below.

- MEDLINE
- Embase
- Epub ahead of print
- MEDLINE In-Process
- The Cochrane Library
    - Central register of controlled trials
    - Database of abstracts of reviews of effects

The searches were conducted using the OVID platform. The OVID platform is an accepted tool in SLRs and provides a standardised access to a wide range of clinical literature databases. Advanced searching techniques were used to increase the efficiency of the search and encompass a series of abbreviated terms (Table A. 2).

Table A. 2: Key search commands for OVID-based searches

Search Commands	Explanation
ab.	Abstract
Dr	Drug Resistance
Dt	Drug Therapy
Exp	Indicates that the Medical Subject Heading (MeSH) was exploded to include the narrower, more specific terms beneath it in the MeSH tree
mp.	Indicates a multi-purpose search (several fields at the time on advanced searches), looking in general into the Title, Original Title, Abstract, Subject Heading, Name of Substance, and Registry Word fields
pt.	Indicates the form of the literature (e.g. Article, book, etc...)
th	Therapy
ti.	Title
tw.	Performs a search in all the fields that contain text words and which are appropriate for a subject search (title and abstract in Medline; title abstract and drug trade name in Embase)
/	Indicates a MeSH subject with all subheadings selected
$	Indicates that the search term was truncated
?	Replaces zero or one character

A.3 Search strategies

Search strategies with the OVID platform were based on specific combinations of thematic groups. Thematic groups encompass all the possible individual search words ("search strings") that refer to, or are related with an overarching topic. For example, "randomised controlled trials" and "double blind procedure" will both be part of the thematic group "RCT study terms".

The timeframe of the search was set from 2000 to 2018 and the language of publication was restricted to English. The original SLR search was conducted on 14 April 2017 and was further updated on 03 April 2018. A schematic overview of the clinical search strategy is given in Table A. 4 and the detailed search strategies are provided in for the searches conducted on 14 April 2017 (Table A. 5) and 03 April 2018 (Table A. 6).

In order to investigate the impact of deviating from the Medicine Council's protocol (not including brand names in the original and updated searches outlined above), the searches were repeated with brand names, over the same time periods as the original and updated clinical SLR; these returned the same number of total records (Table A. 3).

Table A. 3: Comparison of search results in Embase and Medline, with and without brand names

Database	Search	Date limits applied	Date of search	Results with brand names*	Results without brand names
Embase	Original	01/01/2000-14/04/2017	04/10/2018	4161	4161
Embase	Update	14/04/2017-03/04/2018	04/10/2018	801	801
Medline	Original	01/01/2000-14/04/2017	04/10/2018	1211	1211
Medline	update	14/04/2017-03/04/2018	04/10/2018	178	178

* Braftovi, Mektovi, Tafinlar, Mekinist

Table A. 4: Outline clinical search strategy

Clinical Search Strategy
Thematic groups • Disease terms • Intervention and comparator terms • RCT study terms • Observational study terms • Excluded terms
Combinations of thematic groups 1. Disease terms AND intervention & comparator terms AND RCT study terms 2. Disease terms AND intervention & comparator terms AND Observational study terms 3. 1 NOT excluded terms 4. Limit 3 for year (2000-current) and language (English) 5. 2 NOT excluded terms 6. Limit 5 for year (2000-current) and language (English)

Abbreviation: RCT, randomised controlled trial

Table A. 5: Clinical search strategy – Embase, Medline, Cochrane – on 14 April 2017

#	Search term	Hits
Disease terms – metastatic melanoma		
1	exp Melanoma/	191,375
2	melanom$.mp.	247,934
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumo?r$)).ti,ab.	69,292
4	or/1-3	297,332
5	(metasta$ or stage IIIb or stage IIIc or stage IV or unresectable$ or advanced$ or brain metasta$).mp.	1,777,861
6	exp metastasis/dr, dt, th [Drug Resistance, Drug Therapy, Therapy]	49,647
7	5 or 6	1,778,327
8	4 and 7	100,446
Intervention and comparators		
9	dabrafenib.mp. or dabrafenib/	3,108
10	vemurafenib.mp. or vemurafenib/	7,188
11	encorafenib.mp. or encorafenib/	205
12	trametinib.mp. or trametinib/	3,105
13	cobimetinib.mp. or cobimetinib/	585

#	Search term	Hits
14	binimetinib.mp. or binimetinib/	381
15	or/9-14	9,647
16	ipilimumab.mp. or ipilimumab/	9,585
17	nivolumab.mp. or nivolumab/	5,281
18	pembrolizumab.mp. or pembrolizumab/ or lambrolizumab/	4,084
19	atezolizumab.mp. or atezolizumab/	793
20	talimogene.mp. or talimogene/	498
21	or/16-20	14,034
22	(DTIC or dacarbazin$).mp. or dacarbazine/	21,888
23	temozolomide.mp. or temozolomide/	25,571
24	fotemustine.mp. or fotemustine/	1,673
25	vindesine.mp. or vindesine/	6,648
26	paclitaxel.mp. or paclitaxel/	124,813
27	docetaxel.mp. or docetaxel /	66,050
28	cabazitaxel.mp. or cabazitaxel/	2,685
29	carboplatin.mp. or carboplatin/	73,760
30	cisplatin.mp. or cisplatin/	206,822
31	oxaliplatin.mp. or oxaliplatin/	42,418
32	satraplatin.mp. or satraplatin/	797
33	polyplatillen.mp. or polyplatillen/	14
34	(interferon or IFN).mp or interferon/	512,654
35	(interleukin-2 or IL-2).mp or interleukin-2/	172,457
36	melanoma $chemotherapy$.mp.	100
37	or/22-36	1,016,437
38	15 or 21 or 37	1,031,563
Randomized controlled trial terms		
39	Exp Randomized controlled trial/	901,798
40	Exp Randomized controlled trials as topic/	258,349

#	Search term	Hits
41	exp clinical trial/	1,990,520
42	exp clinical trials as topic/	637,785
43	"double blind" procedure/	116,378
44	double-blind method/	358,954
45	"single blind" procedure/	29,404
46	single-blind method/	68,319
47	crossover procedure/	51,695
48	Randomization/	189,920
49	Random allocation/	186,054
50	experimental design/	128,500
51	control group/	276,935
52	Placebo$/	276,337
53	control groups/	277,033
54	clinical trial, phase i.pt.	22,447
55	clinical trial, phase ii.pt.	38,169
56	clinical trial, phase iii.pt.	23,533
57	clinical trial, phase iv.pt.	2,097
58	Randomi?ed controlled trial.pt.	879,557
59	controlled clinical trial.pt.	183,126
60	multicenter stud$.pt.	296,451
61	clinical trial.pt.	799,027
62	(clinical adj3 trial$).mp.	2,425,260
63	randomi?ed controlled trial$.mp.	1,420,314
64	RCT.mp.	53,286
65	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	650,988
66	placebo$.mp.	714,097
67	(random$ adj2 allocat$).mp.	195,826
68	((random$ or control$ or clinical$) adj2 (trial$ or stud$)).mp.	9,146,029

#	Search term	Hits
69	(crossover$ or (cross adj over$)).mp.	229,204
70	or/39-69	9,941,275
71	8 (Disease) and 38 (Intervention/comparators) and 70 (RCT studies)	13,734
Exclusion terms		
72	conference abstract$.mp.	5,110
73	Letter.pt.	1,663,094
74	Letter.mp.	1,718,640
75	congress$.pt.	71,926
76	congress$.mp.	154,058
77	editorial.pt.	885,224
78	review$.pt.	4,096,717
79	review$.mp.	6,076,148
80	conference paper$.mp.	482,992
81	conference proceeding$.mp.	9,916
82	(editorial or note).mp.	1,582,994
83	exp Animal/ not Human/	7,348,125
84	comment$.pt. or comment$.mp.	925,816
85	or/72-84	17,059,860
86	71 not 85	7,622
87	Limit 86 to (English language and yr="2000-Current")	6,471
Observational study terms		
88	exp clinical study/	6,829,615
89	exp case control study/	1,018,389
90	family study/	34,322
91	longitudinal study/	217,845
92	Longitudinal.tw	408,835
93	retrospective study/	1,168,268
94	Retrospective.tw.	963,581

#	Search term	Hits
95	prospective study/	840,265
96	cohort analysis/	536,014
97	(cohort adj (study or studies)).mp.	499,018
98	(Case control adj (study or studies)).tw.	184,882
99	(follow up adj (study or studies)).tw.	88,654
100	(observational adj (study or studies)).tw.	185,454
101	"Cross sectional".tw.	554,924
102	Cross-sectional studies/	319,915
103	or/88-102	9,227,193
104	8 (Disease) and 34 (Intervention & comparator) and 103 (Observational studies)	13,100
105	104 not 85	8,066
106	limit 105 to (english language and yr="2000-Current")	6,770
Total Clinical search		
107	87 (RCT) or 106 (observational study)	8,226

Table A. 6: Clinical search strategy – Embase, Medline, Cochrane – updated on 03 April 2018

#	Search term	Hits
Disease terms – metastatic melanoma		
1	exp Melanoma/	196,436
2	melanom$.mp.	261,745
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumo?r$)).ti,ab.	72,988
4	or/1-3	313,282
5	(metasta$ or stage IIIb or stage IIIc or stage IV or unresectable$ or advanced$ or brain metasta$).mp.	1,897,217
6	exp metastasis/dr, dt, th [Drug Resistance, Drug Therapy, Therapy]	52,763
7	5 or 6	1,898,248
8	4 and 7	107,384
Intervention and comparators		

#	Search term	Hits
9	dabrafenib.mp. or dabrafenib/	3,753
10	vemurafenib.mp. or vemurafenib/	7,962
11	encorafenib.mp. or encorafenib/	283
12	trametinib.mp. or trametinib/	3,932
13	cobimetinib.mp. or cobimetinib/	845
14	binimetinib.mp. or binimetinib/	520
15	or/9-14	11,264
16	ipilimumab.mp. or ipilimumab/	11,771
17	nivolumab.mp. or nivolumab/	9,742
18	pembrolizumab.mp. or pembrolizumab/ or lambrolizumab/	7,623
19	atezolizumab.mp. or atezolizumab/	2,024
20	talimogene.mp. or talimogene/	662
21	or/16-20	21,163
22	(DTIC or dacarbazin$).mp. or dacarbazine/	22,655
23	temozolomide.mp. or temozolomide/	27,712
24	fotemustine.mp. or fotemustine/	1,731
25	vindesine.mp. or vindesine/	6,667
26	paclitaxel.mp. or paclitaxel/	130,499
27	docetaxel.mp. or docetaxel /	69,409
28	cabazitaxel.mp. or cabazitaxel/	3,016
29	carboplatin.mp. or carboplatin/	77,099
30	cisplatin.mp. or cisplatin/	215,272
31	oxaliplatin.mp. or oxaliplatin/	44,981
32	satraplatin.mp. or satraplatin/	790
33	polyplatillen.mp. or polyplatillen/	14
34	(interferon or IFN).mp or interferon/	532,173
35	(interleukin-2 or IL-2).mp or interleukin-2/	177,485
36	melanoma $chemotherapy$.mp.	104

#	Search term	Hits
37	or/22-36	1,058,242
38	15 or 21 or 37	1,079,499
Randomized controlled trial terms		
39	Exp Randomized controlled trial/	904,518
40	Exp Randomized controlled trials as topic/	266,985
41	exp clinical trial/	1,941,967
42	exp clinical trials as topic/	616,571
43	"double blind" procedure/	121,499
44	double-blind method/	368,581
45	"single blind" procedure/	29,483
46	single-blind method/	70,474
47	crossover procedure/	50,505
48	Randomization/	162,845
49	Random allocation/	180,225
50	experimental design/	110,725
51	control group/	112,358
52	Placebo$/	263,605
53	control groups/	112,454
54	clinical trial, phase i.pt.	22,158
55	clinical trial, phase ii.pt.	38,205
56	clinical trial, phase iii.pt.	24,932
57	clinical trial, phase iv.pt.	2,245
58	Randomi?ed controlled trial.pt.	901,084
59	controlled clinical trial.pt.	182,368
60	multicenter stud$.pt.	306,938
61	clinical trial.pt.	788,133
62	(clinical adj3 trial$).mp.	2,589,535
63	randomi?ed controlled trial$.mp.	1,529,672

#	Search term	Hits
64	RCT.mp.	61,067
65	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	681,105
66	placebo$.mp.	744,580
67	(random$ adj2 allocat$).mp.	203,683
68	((random$ or control$ or clinical$) adj2 (trial$ or stud$)).mp.	9,736,369
69	(crossover$ or (cross adj over$)).mp.	240,581
70	or/39-69	10,532,652
71	8 (Disease) and 38 (Intervention/comparators) and 70 (RCT studies)	15,700
Exclusion terms		
72	conference abstract$.mp.	5,574
73	Letter.pt.	1,703,309
74	Letter.mp.	1,759,743
75	congress$.pt.	65,549
76	congress$.mp.	148,569
77	editorial.pt.	925,209
78	review$.pt.	4,260,071
79	review$.mp.	6,364,718
80	conference paper$.mp.	507,524
81	conference proceeding$.mp.	11,007
82	(editorial or note).mp.	1,651,687
83	exp Animal/ not Human/	7,591,007
84	comment$.pt. or comment$.mp.	961,884
85	or/72-84	17,733,299
86	71 not 85	8,574
87	Limit 86 to (English language and yr="2000-Current")	7,478
Observational study terms		
88	exp clinical study/	6,937,386
89	exp case control study/	1,053,243

#	Search term	Hits
90	family study/	22,706
91	longitudinal study/	217,087
92	Longitudinal.tw	444,203
93	retrospective study/	1,277,148
94	Retrospective.tw.	1,066,312
95	prospective study/	882,454
96	cohort analysis/	573,205
97	(cohort adj (study or studies)).mp.	546,082
98	(Case control adj (study or studies)).tw.	195,463
99	(follow up adj (study or studies)).tw.	92,305
100	(observational adj (study or studies)).tw.	208,406
101	"Cross sectional".tw.	613,131
102	Cross-sectional studies/	388,687
103	or/88-102	9,516,477
104	8 (Disease) and 34 (Intervention & comparator) and 103 (Observational studies)	12,021
105	104 not 85	8,456
106	limit 105 to (english language and yr="2000-Current")	7,258
Total Clinical search		
107	87 (RCT) or 106 (observational study)	9,616

A.4 Article eligibility and study selection

All references identified through the OVID searches were imported to the SLR online tool called 'Covidence' and duplicates were removed to evaluate the study for full-text eligibility.

Publications identified through the systematic review were evaluated in a stepwise process in order to assess whether or not they should be included for data extraction. Furthermore, an additional step was foreseen in case uncertainty about inclusion/exclusion of the article existed. This procedure is described in steps 1 to 4, below.

Step 1: Title and abstract review

All publications were independently double reviewed based on their titles first and then abstracts against the inclusion/exclusion criteria. All papers included at the end of this stage were retained for Step 3. Papers excluded at this review stage were reported in a table format with a clear justification for their exclusion and a note of the number of papers excluded was kept for use in the PRISMA flow diagram. All publications included in the review were presented in an excel document with the title, year of publication, authors and abstract provided for review.

Articles for which uncertainty remains whether to include or exclude passed through a second step for reconciliation or arbitrage.

Step 2: Abstracts with uncertain inclusion/exclusion

Publications for which uncertainty exists on the most appropriate action (inclusion or exclusion) after being double reviewed, any disagreement was resolved either through "reconciliation" (discussion between the two reviewers) or through "arbitration" (by a third independent reviewer). In the last case, the "majority view" determined inclusion or exclusion. Retained publications passed to Step 3 (together with those retained in Step 1), whereas excluded publications were maintained in a separate MS Excel file with a clear justification for their exclusion.

Step 3 – Full text review

Publications included after abstract review or step 2 were ordered for a full review of the text by two independent reviewers. All papers included after the full text review were retained for further categorization. A record was kept of papers excluded at this stage along with a clear justification for their exclusion.

Step 4 – Full text with uncertain inclusion/exclusion

The same procedure as described in step 2 was considered for the full texts. Inclusion criteria as well as exclusion criteria are presented in Table A. 7 below.

Table A. 7: Inclusion and exclusion criteria

Inclusion criteria	**Population:** Adult (18 years and older) patients with unresectable or metastatic cutaneous melanoma
	Intervention(s): Encorafenib (combined with) binimetinib, dabrafenib, vemurafenib, trametinib, cobimetinib, ipilimumab, nivolumab, pembrolizumab (lambrolizumab), atezolizumab, talimogene, dacarbazine, temozolomide, fotemustine, vindesine, interferon, interleukin-2, taxanes, platinum derivatives (monotherapy or combination therapy [i.e. 2 drugs or more])
	Comparator(s): Any treatment from the above-mentioned list of interventions (monotherapy or combination therapy [i.e. 2 drugs or more) OR Placebo or best supportive care
	Outcomes: Clinical endpoints: PFS, OS, ORR, CR, PR, TTR, DOR, DCR, BOR, SD, PD *AND/OR* Safety endpoints: rates of treatment-emergent AEs, recurrence rates after treatment, treatment discontinuation due to AE, dose report, dose reduction, grade 3/4, serious AE, dose intensity, dose exposure, type of AE, hospitalisation rate (reason for hospitalisation and duration)
	Settings (if applicable): Not applicable
	Study design: RCT OR Observational studies OR (All studies must include at least 10 patients and 10 patients per comparator arm for RCTs)
	Language restrictions: English
	Other search limits or restrictions applied: The timeframe of the search was set from 2000 to 2018
Exclusion criteria	**Population:** Non-human populations Patients below 18 years Patients with other types of skin cancers (non-melanoma skin cancers), such as basal cell and squamous-cell cancers, Kaposi sarcoma, and lymphoma of the skin
	Intervention(s): Any not listed in the inclusion criteria

	BRAF/MEK inhibitors like sorafenib (who failed to demonstrate its activity in phase III clinical trial in melanoma), selumetinib and pimasertib (whose development was stopped in melanoma) are excluded
	Comparator(s): Any not listed in the inclusion criteria
	Outcomes: Any not listed in the inclusion criteria
	Settings (if applicable): Not applicable
	Study design: Editorials OR Notes OR Comments OR Letters OR Case reports OR Case series OR Systematic reviews OR Conference or congress papers/reviews/proceedings
	Language restrictions: Any not listed in the inclusion criteria
	Other search limits or restrictions applied: Not applicable

AE: adverse event; BOR: best overall response; CR: complete response; DCR: disease control rate; DOR: duration of response; ORR: objective/overall response rate; OS: overall survival; PD: progressed disease; PFS: progression free survival; PR: partial response; RCT: randomised controlled trial; SD: stable disease; TTR: time to response

A.5 Classification of included articles

All included studies were classified based on trial design (randomised controlled trial [RCT] or non-RCT) and treatment (BRAF inhibitor, immuno-oncology [IO] therapy or other) into the following priority categories as per their approval status in the EU [1] and/or recommendations in the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for multiple melanoma [2]:

Priority 1 – RCTs in targeted therapies at doses approved in the EU

RCTs with one of following interventions: Encorafenib (combined with) binimetinib, dabrafenib monotherapy, vemurafenib monotherapy, dabrafenib in combination with trametinib, vemurafenib in combination with cobimetinib. These studies were included in priority 1 only if they were conducted in the EMA approved dose of these interventions.

Priority 2 – RCTs in IO therapies at doses approved in the EU

RCTs with one of following interventions: Ipilimumab monotherapy, nivolumab monotherapy, pembrolizimab monotherapy, ipilimumab in combination with nivolumab. These studies were included in priority 2 only if they were conducted in the EMA approved dose of these interventions.

Priority 3 – Non-RCTs in targeted therapies

Non-RCTs with one of the following interventions: Encorafenib (combined with) binimetinib, dabrafenib monotherapy, vemurafenib monotherapy, dabrafenib in combination with trametinib, vemurafenib in combination with cobimetinib. Priority 3 also included RCTs where these targeted therapies were assessed at doses not approved in EMA.

Priority 4 – Non-RCTs in IO therapies

Non-RCTs with one of the following interventions: Ipilimumab monotherapy, nivolumab monotherapy, pembrolizimab monotherapy, ipilimumab in combination with nivolumab. RCTs and non-RCTs in other IO therapies, such as lambrolizumab and atezolizumab. Priority 4 also included RCTs where these IO therapies were assessed at doses not approved in EMA.

Priority 5 – RCTs in other treatments available for MM

RCTs with one of following interventions: talimogene, dacarbazine, temozolomide, fotemustine, vindesine, interferon, interleukin-2, taxanes and platinum derivatives.

Priority 6 – Non-RCTs in other treatments available for MM

Non-RCTs with one of following interventions: talimogene, dacarbazine, temozolomide, fotemustine, vindesine, interferon, interleukin-2, taxanes and platinum derivatives

Additionally, the studies from priority 3, 4, and 6 are categorised under predictor studies reporting the factors of treatment response or survival outcomes in advanced melanoma patients.

A.6 Quality assessment strategy

The methodological quality of the priority 1 and 2 studies included from the systematic review was assessed using the quality assessment criteria for the National institute for health and care excellence evidence submissions [3] and the Cochrane Risk of Bias tool [4].

The aim of critical assessment is to evaluate the internal and external validity of studies. The framework assesses the potential for studies to be impacted by biases affecting validity, including:

- **Allocation bias**, resulting from a systematic difference (other than the intervention) between experimental and control groups in a clinical trial. Allocation bias can be avoided by appropriate randomisation
- **Patient selection bias**, arising from systematic differences between comparison groups in terms of performance and prognosis, may arise from inadequate concealment of allocation
- **Performance bias**, relative to the provision of systematically different care other than the intervention between comparison groups, arising from care givers or participants acting differently

because they know which intervention is being delivered and not being blind to treatment allocation

- **Attrition bias** arising from systematic differences between comparison groups in how participants are withdrawn or excluded from the study groups
- **Detection and reporting bias**, arising from systematic differences in how outcomes are ascertained and measured and/or reported
- **Exclusion bias** may occur due to the exclusion of patients from the analysis. An intention-to-treat (ITT) analysis is generally recommended for reducing it

A checklist was used to assess the quality of each study included in the review with respect to methodological criteria for experimental studies.

A.7 Results

A summary of results for the search conducted on 14 April 2017 and 3 April 2018 are outlined in section 4.2.1 of the main document.

A.7.1 List of included studies

A list of priority 1 studies (BRAFi RCTs) is provided below. Although the scope for priority 1 studies was broader than the PICO defined by the Medicine Council, incorporating all BRAFi monotherapies and combination therapies, all studies pertaining to the intervention (Enco+Bini 450) and the comparator (Dabra+Tram) were captured in the COLUMBUS, COMBI-v and COMBI-d trials.

COLUMBUS

1. Primary: Dummer et al, 2018 [5]
    - Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018.
2. Dummer et al, 2018 (abstract) [6]
    - Dummer R, et al. Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma. J Clin Oncol. 2018;36:9504-.
3. Gogas et al, 2018 (abstract) [7]
    - Gogas HJ, Dummer R, Ascierto PA, et al. Adverse Events of Special Interest in the Phase 3 COLUMBUS Study. J Clin Oncol. 2018;36:9567-.

COMBI-v

4. Primary: Robert et al, 2015 [8]
    - Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372(1):30-9.

5. Robert et al, 2016 (abstract) [9]

    - Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroyakovskiy D, et al. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. Ann Oncol. 2016;27(Suppl_6):LBA40.

COMBI-d

6. Primary: Long et al, 2017 [10]

    - Long GV, Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol. 2017;28(7):1631-9

7. Long et al, 2014 [11]

    - Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877-88.

8. Long et al, 2015 [12]

    - Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444-51.

BRF113220 Part C

9. Primary: Long et al, 2018 [13]

    - Long GV, Eroglu Z, Infante J, Patel S, Daud A, Johnson DB, et al. Long-Term Outcomes in Patients With BRAF V600-Mutant Metastatic Melanoma Who Received Dabrafenib Combined With Trametinib. J Clin Oncol. 2018;36(7):667-73.

10. Flaherty et al, 2012 [14]

    - Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012;367(18):1694-703.

11. Flaherty et al, 2014 (abstract) (12)

    - Flaherty K, Daud A, Weber JS, Sosman JA, Kim K, Gonzalez R, et al. Updated overall survival (OS) for BRF113220, a phase 1-2 study of dabrafenib (D) alone versus combined dabrafenib and trametinib (D+T) in pts with BRAF V600 mutation-positive (+) metastatic melanoma (MM). Journal of Clinical Oncology. 2014;32:9010-.

12. Latimer et al, 2015 [15]

    - Latimer NR, Amonkar MM, Stapelkamp C, Sun P. Adjusting for confounding effects of treatment switching in a randomized phase II study of dabrafenib plus trametinib in BRAF V600+ metastatic melanoma. Melanoma Research. 2015;25:528–36.

13. Long et al, 2016 [16]

- Long GV, Weber JS, Infante JR, Kim KB, Daud A, Gonzalez R, et al. Overall survival and durable responses in patients with BRAF V600–mutant metastatic melanoma receiving dabrafenib combined with trametinib. Journal of Clinical Oncology. 2016;34:871-8.

CoBRIM

14. Primary: Ascierto et al, 2016 [17]

- Ascierto PA, McArthur GA, Dreno B, Atkinson V, Liszkay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016;17(9):1248-60.

15. Larkin et al, 2014 [18]

- Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371(20):1867-76.

16. Dreno et al, 2017 [19]

- Dreno B, Ribas A, Larkin J, Ascierto PA, Hauschild A, Thomas L, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. Ann Oncol. 2017;28(5):1137-44.

BREAK-3

17. Primary: Hauschild et al, 2012 [20]

- Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358-65.

18. Hauschild et al, 2013 (abstract) [21]

- Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. An update on BREAK-3, a phase III, randomized trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM). Journal of Clinical Oncology. 2013;31:9013-.

19. Latimer et al, 2015 [22]

- Latimer NR, Abrams KR, Amonkar MM, Stapelkamp C, Swann RS. Adjusting for the Confounding Effects of Treatment Switching - The BREAK-3 Trial: Dabrafenib Versus Dacarbazine. The Oncologist. 2015;20:798-805.

BRIM-3

20. Primary: Chapman et al, 2017 [23]

- Chapman PB, Robert C, Larkin J, Haanen JB, Ribas A, Hogg D, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. Ann Oncol. 2017;28(10):2581-7.

21. Chapman et al, 2011[24]

- Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507-16.

22. McArthur et al, 2014 [25]

- McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014;15(3):323-32.

23. Hauschild et al, 2016 (abstract) [26]

- Ugurel S, Rohmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer. 2017;83:247-57.

Note that abstract could not be accessed; data was taken from this publication where the abstract has been cross-referenced.

A.7.2 List of excluded studies (based on full-text review)

The list of excluded studies, following full text review, including reasons for exclusion are provided in separate document entitled: PF_EncoBini_SLR_QoL_Clinical_Excluded_studies.xlsx

A list of the 194 citations excluded at full text review is also provided below:

1. Aamdal, S.; Wolchock, J. D.; Weber, J.; Hamid, O.; O'Day, S.; Schmidt, H.; Berman, D.; Chasalow, S. D. Changes in peripheral blood absolute lymphocyte count (ALC) may guide patient selection for continued treatment with ipilimumab 2009 European Journal of Cancer, Supplement 7 (2-3) 579

2. Abraham, J. Ipilimumab improves survival in previously treated metastatic melanoma 2010 Community Oncology 7 9 395-396

3. Agarwala, S. S.; Glaspy, J.; O'Day, S. J.; Mitchell, M.; Gutheil, J.; Whitman, E.; Gonzalez, R.; Hersh, E.; Feun, L.; Belt, R.; Meyskens, F.; Hellstrand, K.; Wood, D.; Kirkwood, J. M.; Gehlsen, K. R.; Naredi, P. Results from a randomized phase III study comparing combined treatment with histamine dihydrochloride plus interleukin-2 versus interleukin-2 alone in patients with metastatic melanoma 2002 Journal of Clinical Oncology 20 1 125-133

4. Akman, T.; Oztop, I.; Baskin, Y.; Akbarpour, M.; Unal, O. U.; Oflazoglu, U.; Ellidokuz, H. The role of BRAF mutation in patients with high-risk malignant melanoma treated with high-dose adjuvant interferon therapy 2015 Medical Oncology 32 1 1-10

5. Akman, T.; Oztop, I.; Baskin, Y.; Akbarpour, M.; Unal, O. U.; Oflazoglu, U.; Ellidokuz, H.; Lebe, B. The role of BRAF mutation in patients with high-risk malignant melanoma treated with high-dose adjuvant interferon therapy.[Erratum appears in Med Oncol. 2015 Mar;32(3):62 Note: Lebe, Banu [added]] 2015 Medical Oncology 32 1 440

6. Akman, T.; Oztop, I.; Unek, I. T.; Koca, D.; Unal, O. U.; Salman, T.; Yavuzsen, T.; Yilmaz, A. U.; Somali, I.; Demir, N.; Ellidokuz, H. Long-term outcomes and prognostic factors of high-risk malignant melanoma patients after surgery and adjuvant high-dose interferon treatment: A single-center experience 2014 Chemotherapy 60 4 228-238

7. Albertini, M. R.; Hank, J. A.; Gadbaw, B.; Kostlevy, J.; Haldeman, J.; Schalch, H.; Gan, J.; Kim, K.; Eickhoff, J.; Gillies, S. D.; Sondel, P. M. Phase II trial of hu14.18-IL2 for patients with metastatic melanoma 2012 Cancer Immunology, Immunotherapy 61 12 2261-71

8. Alexander Jr, H. R.; Fraker, D. L.; Bartlett, D. L.; Libutti, S. K.; Steinberg, S. M.; Soriano, P.; Beresnev, T. Analysis of factors influencing outcome in patients with in-transit malignant melanoma undergoing isolated limb perfusion using modern treatment parameters 2010 Journal of Clinical Oncology 28 1 114-118

9. Altomonte, M.; Queirolo, P.; Testori, A.; Ascierto, P.; Danielli, R.; Di Giacomo, A. M.; Chiarion Sileni, V.; Del Vecchio, M.; Ridolfi, R.; Maio, M. The Italian experience on the feasibility and safety of ipilimumab therapy in pretreated metastatic melanoma patients 2009 European Journal of Cancer, Supplement 7 (2-3) 585

10. Amaravadi, R. K.; Schuchter, L. M.; McDermott, D. F.; Kramer, A.; Giles, L.; Gramlich, K.; Carberry, M.; Troxel, A. B.; Letrero, R.; Nathanson, K. L.; Atkins, M. B.; O'Dwyer, P. J.; Flaherty, K. T. Phase II trial of temozolomide and sorafenib in advanced melanoma patients with or without brain metastases 2009 Clinical Cancer Research 15 24 7711-8

11. Amaria, R. N.; Bassett, R. L.; Simpson, L.; Delaney, F.; Hwu, P.; Kim, K.; Hwu, W. J.; Patel, S. P.; Glitza, I. C.; Davies, M. A.; Woodman, S. E.; Yee, C.; Bedikian, A. Y. Phase I study of ipilimumab (IPI) with biochemotherapy (BCT) for chemonaive patients with metastatic melanoma (MM) 2015 Journal of Clinical Oncology. Conference 33 15 SUPPL. 1

12. Anaya, D. A.; Xing, Y.; Feng, L.; Huang, X.; Camacho, L. H.; Ross, M. I.; Gershenwald, J. E.; Lee, J. E.; Mansfield, P. F.; Cormier, J. N. Adjuvant high-dose interferon for cutaneous melanoma is most beneficial for patients with early stage III disease 2008 Cancer 112 9 2030-2037

13. Andersson, R.; Ake Hofer, P.; Riklund-Ahlstrom, K.; Henriksson, R. Effects of interferon-alpha, verapamil and dacarbazine in the treatment of advanced malignant melanoma 2003 Melanoma Research 13 1 87-91

14. Andtbacka, R. H. I.; Kaufman, H.; Collichio, F.; Amatruda, T.; Nemunaitis, J.; Chesney, J.; Puzanov, I.; Harrington, K.; Zhang, Y.; Chen, L.; Shilkrut, M.; Ross, M. Durable complete responses (CR) in patients (pts) with stage IIIB-IV melanoma treated with talimogene laherparepvec (T-VEC) in OPTiM 2015 European Journal of Cancer 51 S676

15. Andtbacka, R. H.; Kaufman, H. L.; Frances, C. A.; Delman, K.; Zager, J. S.; Hsueh, E.; Chen, L.; Shilkrut, M.; Ross, M. Lower risk of visceral/bone metastasis (VM) in patients with stage IIIB/C/IVM1a melanoma treated with talimogene laherparepvec (T-VEC) versus GM-CSF in OPTiM (NCT00769704) 2015 Annals of Surgical Oncology 1) S23

16. Andtbacka, R.; Kaufman, H.; Collichio, F.; Amatruda, T.; Nemunaitis, J.; Chesney, J.; Puzanov, I.; Harrington, K.; Zhang, Y.; Chen, L.; Shilkrut, M.; Ross, M. Durable complete responses (CRS) in patients (PTS) with stage IIIb-IV melanoma treated with talimogene laherparepvec (T-VEC) in OPTiM 2016 Annals of Surgical Oncology 1) S31-S32

17. Andtbacka, R.; Kaufman, H.; Harrington, K.; Middleton, M.; Melcher, A.; Ottensmeier, C.; Safaei, R.; Downey, G.; He, P.; Collichio, F. Timing of onset and resolution of adverse events in patients with unresectable stage IIIB-IVM1a melanoma treated with talimogene laherparepvec (T-VEC) in OPTiM 2016 Melanoma Research 26 e36-e37

18. Anonymous, Erratum: Correction to Lancet Oncol 2016; 17: 953 (The Lancet Oncology (2016) 17(7) (943-955) (S1470204516301267) (10.1016/S1470-2045(16)30126-7)) 2016 The Lancet Oncology 17 7 e270

19. Anonymous, Erratum: Association of pembrolizumab with tumor response and survival among patients with advanced melanoma (JAMA - Journal of the American Medical Association (2016) 315:15 (1600-1609)) 2016 JAMA - Journal of the American Medical Association 315 22 2472

20. Anonymous, Vemurafenib. Value unclear in metastatic melanoma 2012 Prescrire International 21 133 288-290

21. Ascierto, P. A.; Chiarion Sileni, V.; Del Vecchio, M.; Altomonte, M.; De Galitiis, F.; Ridolfi, L.; Cognetti, F.; Testori, A.; Bernengo, M. G.; Queirolo, P. The european ipilimumab expanded access programme (EAP): Efficacy and safety data from the Italian cohort of patients with pretreated, advanced melanoma 2012 Annals of Oncology 23 ix367-ix368

22. Ascierto, P. A.; Dreno, B.; Larkin, J.; McArthur, G.; Danielli, R.; Demidov, L.; Park, E.; Gilberg, F.; Antic, V.; Ribas, A. Clinical predictors of survival with cobimetinib (C) combined with vemurafenib (V): Pooled analysis from BRIM7 and coBRIM 2017 Pigment Cell and Melanoma Research 30 (1) 81

23. Ascierto, P. A.; Giacomo, A. M. D.; Rutkowski, P.; Vecchio, M. D.; Thomas, L.; Hogg, D.; Queirolo, P.; Bozon, V.; Sandor, V.; Dummer, R.; Long, G. V. Management of MEK inhibitor (MEKi) toxicities of binimetinib (BINI) in the NEMO trial 2017 Pigment Cell and Melanoma Research 30 (1) 81-82

24. Ascierto, P. A.; Leonardi, E.; Ottaiano, A.; Napolitano, M.; Scala, S.; Castello, G. Prognostic value of serum VEGF in melanoma patients: A pilot study 2004 Anticancer Research 24 6 4255-4258

25. Ascierto, P. A.; McArthur, G. A.; Dreno, B.; Larkin, J.; Liszkay, G.; Maio, M.; Mandala, M.; Demidov, L.; Stroyakovskiy, D.; Thomas, L.; de la Cruz-Merino, L.; Atkinson, V.; Dutriaux, C.; Garbe, C.; Chang, I.; Hack, S. P.; Ribas, A. coBRIM: A phase 3, double-blind, placebo-controlled study of vemurafenib versus vemurafenib + cobimetinib in previously untreated BRAF ^{V600} mutation-positive patients with unresectable locally advanced or metastatic melanoma (NCT01689519) 2015 Journal of Translational Medicine 1-2

26. Atkins, M. B.; Gollob, J. A.; Sosman, J. A.; McDermott, D. F.; Tutin, L.; Sorokin, P.; Parker, R. A.; Mier, J. W. A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, temozolomide, interleukin 2, and IFN-alpha2B in patients with metastatic melanoma 2002 Clinical Cancer Research 8 10 3075-3081

27. Atkins, M. B.; Hsu, J.; Lee, S.; Cohen, G. I.; Flaherty, L. E.; Sosman, J. A.; Sondak, V. K.; Kirkwood, J. M. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): A trial coordinated by the Eastern Cooperative Oncology Group 2008 Journal of Clinical Oncology 26 35 5748-5754

28. Atkins, M. B.; Sosman, J. A.; Agarwala, S.; Logan, T.; Clark, J. I.; Ernstoff, M. S.; Lawson, D.; Dutcher, J. P.; Weiss, G.; Curti, B.; Margolin, K. A. Temozolomide, thalidomide, and whole brain radiation therapy for patients with brain metastasis from metastatic melanoma: A phase II cytokine working group study 2008 Cancer 113 8 2139-2145

29. Atzpodien, J.; Neuber, K.; Kamanabrou, D.; Fluck, M.; Brocker, E. B.; Neumann, C.; Runger, T. M.; Schuler, G.; Von den Driesch, P.; Muller, I.; Paul, E.; Patzelt, T.; Reitz, M. Combination chemotherapy with or without s.c. IL-2 and IFN-alpha: Results of a prospectively randomized trial of the cooperative advanced malignant melanoma chemoimmunotherapy group (ACIMM) 2002 British Journal of Cancer 86 2 179-184

30. Atzpodien, J.; Terfloth, K.; Fluck, M.; Reitz, M. Age has no significant impact on overall survival and on treatment tolerability in relapsed stage IV cutaneous malignant melanoma patients receiving cisplatin, gemcitabine, and treosulfan 2011 American Journal of Clinical Oncology: Cancer Clinical Trials 34 1 2-5

31. Atzpodien, J.; Terfloth, K.; Fluck, M.; Reitz, M. Cisplatin, gemcitabine, and treosulfan in relapsed stage IV cutaneous malignant melanoma patients 2007 British Journal of Cancer 97 10 1329-1332

32. Awada, A.; Gil, T.; Sales, F.; Dubuisson, M.; Vereecken, P.; Klastersky, J.; Moerman, C.; De Valeriola, D.; Piccart, M. J. Prolonged schedule of temozolomide (Temodal) plus liposomal doxorubicin (Caelyx) in advanced solid cancers 2004 Anti-Cancer Drugs 15 5 499-502

33. Babovic, N.; Matkovic, S.; Ursulovic, T.; Kreacic, M.; Milosavljevic, M.; Jelic, S. Randomized phase II study of dacarbazine (DTIC) with or without carboplatin (CBDCA) in patients with stage IV cutaneous melanoma 2008 Annals of Oncology 19 (S8) viii241

34. Banfalvi, T.; Boldizsar, M.; Gergye, M.; Gilde, K.; Kremmer, T.; Otto, S. Comparison of prognostic significance of serum 5-S-cysteinyldopa, LDH and S-100B protein in stage III-IV malignant melanoma 2002 Pathology and Oncology Research 8 3 183-187

35. Banfalvi, T.; Gilde, K.; Boldizsar, M.; Kremmer, T. Clinical significance of 5-S-cysteinyldopa monitoring in patients with malignant melanoma 2002 Neoplasma 49 2 121-125

36. Beasley, G. M.; Speicher, P.; Augustine, C. K.; Dolber, P. C.; Peterson, B. L.; Sharma, K.; Mosca, P. J.; Royal, R.; Ross, M.; Zager, J. S.; Tyler, D. S. A Multicenter Phase I Dose Escalation Trial to Evaluate Safety and Tolerability of Intra-arterial Temozolomide for Patients with Advanced Extremity Melanoma Using Normothermic Isolated Limb Infusion 2015 Annals of Surgical Oncology 22 1 287-294

37. Bedane, C.; Leccia, M. T.; Sassolas, B.; Bregman, B.; Lebbe, C. Treatment patterns and outcomes in patients with advanced melanoma in France 2013 Current Medical Research and Opinion 29 10 1297-1305

38. Bedikian, A. Y.; Millward, M.; Pehamberger, H.; Conry, R.; Gore, M.; Trefzer, U.; Pavlick, A. C.; DeConti, R.; Hersh, E. M.; Hersey, P.; Kirkwood, J. M.; Haluska, F. G. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: The oblimersen melanoma study group 2006 Journal of Clinical Oncology 24 29 4738-4745

39. Bernengo, M. G.; Quaglino, P.; Cappello, N.; Lisa, F.; Osella-Abate, S.; Fierro, M. T. Macrophage-mediated immunostimulation modulates therapeutic efficacy of interleukin-2 based chemoimmunotherapy in advanced metastatic melanoma patients 2000 Melanoma Research 10 1 55-65

40. Birkeland, E.; Busch, C.; Berge, E. O.; Geisler, J.; Jonsson, G.; Lillehaug, J. R.; Knappskog, S.; Lonning, P. E. Low BRAF and NRAS expression levels are associated with clinical benefit from DTIC therapy and prognosis in metastatic melanoma 2013 Clinical and Experimental Metastasis 30 7 867-876

41. Bjoern, J.; Iversen, T. Z.; Nitschke, N. J.; Andersen, M. H.; Svane, I. M. Safety, immune and clinical responses in metastatic melanoma patients vaccinated with a long peptide derived from indoleamine 2,3-dioxygenase in combination with ipilimumab 2016 Cytotherapy 18 8 1043-1055

42. Blanco Codesido, M.; Tesainer Brunetto, A.; Frentzas, S.; Moreno Garcia, V.; Papadatos-Pastos, D.; Pedersen, J. V.; Trani, L.; Puglisi, M.; Molife, L. R.; Banerji, U. Outcomes of patients with metastatic melanoma treated with molecularly targeted agents in phase I clinical trials 2011 Oncology 81 2 135-140

43. Boasberg, P. D.; Hoon, D. S. B.; Piro, L. D.; Martin, M. A.; Fujimoto, A.; Kristedja, T. S.; Bhachu, S.; Ye, X.; Deck, R. R.; O'Day, S. J. Enhanced survival associated with vitiligo expression during

maintenance biotherapy for metastatic melanoma 2006 Journal of Investigative Dermatology 126 12 2658-2663

44. Brohl, A. S.; Khushalani, N. I.; Eroglu, Z.; Markowitz, J.; Thapa, R.; Chen, Y. A.; Kudchadkar, R.; Weber, J. S. A phase ib study of ipilimumab with peginterferon alfa-2b in patients with unresectable melanoma 2016 Journal for ImmunoTherapy of Cancer 4 (1) (no pagination) 85

45. Bucheit, A. D.; Joseph, R. W.; Milton, D.; Fox, P.; Bassett, R.; Gershenwald, J. E.; Tetzlaff, M. T.; Prieto, V. G.; Lazar, A. J.; Davies, M. A. PTEN loss correlates with shorter time to brain metastasis and overall survival in stage IIIB/C melanoma patients 2013 European Journal of Cancer 49 S872-S873

46. Bukowski, R.; Ernstoff, M. S.; Gore, M. E.; Nemunaitis, J. J.; Amato, R.; Gupta, S. K.; Tendler, C. L. Pegylated interferon alfa-2b treatment for patients with solid tumors: A phase I/II study 2002 Journal of Clinical Oncology 20 18 3841-3849

47. Cao, M. G.; Arance, A.; Piulats, J. M.; Marquez, I.; Manzano, J. L.; Berrocal, A.; Crespo, G.; Rodriguez, D.; Perez, E.; Berciano, M.; Soria, A.; Castano, A. G.; Espinosa, E.; Montagut, C.; Lorenzo, A.; Puertolas, T.; Aguado, C.; Royo, M. A.; Blanco, R.; Rodriguez, J. F.; Munoz-Couselo, E.; Mut, P.; Barron, F.; Martin-Algarra, S. Results of the Spanish EAP of pembrolizumab in melanoma. Spanish Melanoma Group (GEM) 2017 Pigment Cell and Melanoma Research 30 (1) 119

48. Cao, M. G.; Malvehy, J.; Marti, R.; Conill, C.; Sanchez, M.; Martin, M.; Carrera, C.; Herrero, J.; Gascon, P.; Mellado, B.; Castel, T.; Puig, S. Biochemotherapy with temozolomide, cisplatin, vinblastine, subcutaneous interleukin-2 and interferon-alpha in patients with metastatic melanoma 2006 Melanoma Research 16 1 59-64

49. Carlino, M. S.; Fung, C.; Shahheydari, H.; Todd, J. R.; Boyd, S. C.; Irvine, M.; Nagrial, A. M.; Scolyer, R. A.; Kefford, R. F.; Long, G. V.; Rizos, H. Preexisting MEK1^{P124} mutations diminish response to BRAF inhibitors in metastatic melanoma patients 2015 Clinical Cancer Research 21 1 98-105

50. Carneiro, F.; Godinho, J.; Sousa, N.; Ferreira, P.; Raimundo, A.; Rodrigues, H. Dacarbazine as first line treatment of metastatic melanoma in elderly patients 2011 European Journal of Cancer 47 S279-S280

51. Characiejus, D.; Pasukoniene, V.; Auskaite, R. J.; Azlauskaite, N.; Aleknavicius, E.; Mauricas, M.; Den Otter, W. Peripheral blood CD8highCD57+ lymphocyte levels may predict outcome in melanoma patients treated with adjuvant interferon-alpha 2008 Anticancer Research 28 2 B 1139-1142

52. Chasset, F.; Pages, C.; Biard, L.; Roux, J.; Sidina, I.; Madelaine, I.; Basset-Seguin, N.; Viguier, M.; Madjlessi, N.; Schneider, P.; Bagot, M.; Resche-Rigon, M.; Lebbe, C. Single-center experience in French Temporary Authorization for Use (TAU) metastatic melanoma program with ipilimumab 2014 Journal of Clinical Oncology. Conference 32 15 SUPPL. 1

53. Chesney, J.; Collichio, F.; Andtbacka, R.; Puzanov, I.; Glaspy, J.; Milhem, M.; Hamid, O.; Cranmer, L.; Saenger, Y.; Ross, M.; Chen, L.; Kim, J. J.; Kaufman, H. L. Interim analysis of a randomized, open-label phase 2 study of talimogene laherparepvec (T) and ipilimumab (I) versus I alone in unresected, stage IIIB-IV melanoma 2017 Pigment Cell and Melanoma Research 30 (1) 90

54. Chiarion Sileni, V.; Hoos, A.; Ibrahim, R.; Maio, M.; Pehamberger, H.; Wolchok, J.; Humphrey, R.; O'Day, S. Prolonged stable disease in ipilimumab-treated patients with advanced melanoma who have progressed on prior anticancer therapies 2008 Annals of Oncology 19 (S8) viii239

55. Clark, J. M.; Kelley, B.; Titze, J.; Fung, H.; Maclejewski, J.; Nathan, S.; Rich, E.; Basu, S.; Kaufman, H. L. Clinical and safety profile of high-dose interleukin-2 treatment in elderly patients with metastatic melanoma and renal cell carcinoma 2013 Oncology (Switzerland) 84 2 123-126

56. Coker, S. A.; Dandamudi, U. B.; Beelen, A. P.; Crosby, N. A.; Fisher, J. L.; Obrocea, M.; Ernstoff, M. S.; Lewis, L. D. A phase I, dose-escalation study of cyclical weekly oral temozolomide and weekly PEG-interferon alpha-2b in patients with refractory or advanced solid tumours 2013 Journal of Chemotherapy 25 6 362-368

57. Conill, C.; Gonzalez-Cao, M.; Jorcano, S.; Puig, S.; Malvehy, J.; Marti, R.; Castel, T. Temozolomide as prophylaxis for melanoma brain metastases 2004 Melanoma Research 14 1 73-4

58. Coupe, N.; Corrie, P.; Hategan, M.; Larkin, J.; Gore, M.; Gupta, A.; Wise, A.; Suter, S.; Ciria, C.; Love, S.; Collins, L.; Middleton, M. R. PACMEL: A phase 1 dose escalation trial of trametinib (GSK1120212) in combination with paclitaxel 2015 European Journal of Cancer 51 3 359-366

59. Cybulska-Stopa, B.; Skoczek, M.; Ziobro, M.; Switaj, T.; Falkowski, S.; Morysinski, T.; Hetnal, M.; Cedrych, I.; Rutkowski, P. Results of systemic treatment of cutaneous melanoma in inoperable stage III and IV 2012 Wspolczesna Onkologia 16 6 532-545

60. De Felice, K. M.; Markovic, S.; Kottschade, L. A.; Finnes, H. D.; Loftus, E. V.; Raffals, L. H. Ipilimumab-induced colitis in patients with metastatic melanoma 2014 Gastroenterology 1) S-604

61. Di Giacomo, A. M.; Ascierto, P. A.; Pittiglio, E.; Queirolo, P.; Pilla, L.; Ridolfi, R.; Santinami, M.; Testori, A.; Parmiani, G.; Maio, M. A phase II study combining Ipilimumab and fotemustine in patients with metastatic Melanoma - The NIBIT-M1 trial 2011 European Journal of Cancer 47 S653-S654

62. Di Giacomo, A. M.; Danielli, R.; Calabro, L.; Bertocci, E.; Nannicini, C.; Miracco, C.; Biagioli, M.; Mazzei, M. A.; Altomonte, M.; Maio, M. Ipilimumab in the common daily practice: Feasibility, safety, efficacy and long-term follow-up in heavily pretreated metastatic melanoma patients 2009 European Journal of Cancer, Supplement 7 (2-3) 585

63. Di Giacomo, A. M.; Maio, M. A randomized, phase III study of fotemustine versus the combination of fotemustine and ipilimumab or the combination of ipilimumab and nivolumab in patients with melanoma with brain metastasis: The NIBIT-M2 study 2015 Annals of Oncology 26 viii5

64. Di Giacomo, A.; Danielli, R.; Calabro, L.; Guidoboni, M.; Miracco, C.; Biagioli, M.; Mazzei, M.; Altomonte, M.; Maio, M. Ipilimumab in the common daily practice: Feasibility, safety, and efficacy in heavily pretreated metastatic melanoma patients 2009 Journal of Clinical Oncology 1) e20002

65. Dika, E.; Patrizi, A.; Fanti, P. A.; Piraccini, B. M. Hair and nail adverse events during treatment with target therapies for metastatic melanoma 2016 Journal of the American Academy of Dermatology 1) AB135

66. Dillman, R. O.; Depriest, C.; McClure, S. E. High-dose IL2 in metastatic melanoma: Better survival in patients immunized with antigens from autologous tumor cell lines 2014 Cancer Biotherapy and Radiopharmaceuticals 29 2 53-57

67. D'Mello S, A. N.; Flanagan, J. U.; Green, T. N.; Leung, E. Y.; Askarian-Amiri, M. E.; Joseph, W. R.; McCrystal, M. R.; Isaacs, R. J.; Shaw, J. H. F.; Furneaux, C. E.; During, M. J.; Finlay, G. J.; Baguley, B. C.; Kalev-Zylinska, M. L. Evidence that GRIN2A mutations in melanoma correlate with decreased survival 2014 Frontiers in Oncology 4 JAN (no pagination) Article 333

68. Du Four, S.; Wilgenhof, S.; Neyns, B. Ipilimumab in patients with melanoma brain metastases, a single-center experience in an expanded access program 2012 Neuro-Oncology 14 iii79

69. Dummer, R.; Flaherty, K.; Kefford, R.; Ascierto, P. A.; Moutouh-de Parseval, L.; Wasserman, E.; Schadendorf, D. The development of the BRAF inhibitor encorafenib (LGX818) and mitogen-activated protein kinase inhibitor binimetinib (MEK162) in patients with metastatic melanoma 2014 British Journal of Dermatology 171 67-68

70. Dummer, R.; Goldinger, S.; Turtschi, C.; Eggmann, N.; Michielin, O.; Mitchell, L.; Veronese, L.; Hilfiker, P. R.; Rinderknecht, J. D. Open-label pilot study of vemurafenib in previously treated metastatic melanoma (MM) patients (PTS) with symptomatic brain metastases (BM) 2012 Annals of Oncology 23 ix366

71. Dummer, R.; Rochlitz, C.; Velu, T.; Acres, B.; Limacher, J. M.; Bleuzen, P.; Lacoste, G.; Slos, P.; Romero, P.; Urosevic, M. Intralesional adenovirus-mediated interleukin-2 gene transfer for advanced solid cancers and melanoma 2008 Molecular Therapy 16 5 985-994

72. Dummer, R.; Sandhu, S.; Hassel, J. C.; Munoz, E.; Berking, C.; Gesierich, A.; Ascierto, P. A.; Esposito, O.; Carter, K.; Antona, V.; Radhakrishnan, R.; Cui, X.; Caponigro, G.; Jaeger, S.; Demuth, T.; Miller Jr, W. H. LOGIC2: Phase 2, multi-center, open-label study of sequential encorafenib/binimetinib combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally-advanced or metastatic BRAF V600 melanoma 2015 European Journal of Cancer 51 S667-S668

73. Eigentler, T. K.; Radny, P.; Hauschild, A.; Gutzmer, R.; Linse, R.; Pfohler, C.; Wagner, S. N.; Schadendorf, D.; Ellwanger, U.; Garbe, C. Adjuvant treatment with vindesine in comparison to observation

alone in patients with metastasized melanoma after complete metastasectomy: A randomized multicenter trial of the German Dermatologic Cooperative Oncology Group 2008 Melanoma Research 18 5 353-358

74. Eisenbeis, C. F.; Lesinski, G. B.; Anghelina, M.; Parihar, R.; Valentino, D.; Liu, J.; Nadella, P.; Sundaram, P.; Young, D. C.; Sznol, M.; Walker, M. J.; Carson, Iii W. E. Phase I study of the sequential combination of interleukin-12 and iterferon afa-2b in advanced cancer: Evidence for modulation of interferon signaling pathways by interleukin-12 2005 Journal of Clinical Oncology 23 34 8835-8844

75. Fateh, S.; Schell, T. D.; Gingrich, R.; Neves, R. I.; Drabick, J. J. Unsuccessful high dose IL-2 therapy followed immediately by near continuous low dose temozolomide can result in rapid durable complete and near-complete remissions in metastatic melanoma 2010 Cancer Biology and Therapy 10 11 1091-1097

76. Feun, L. G.; Savaraj, N.; Hurley, J.; Marini, A. Phase II trial of Paclitaxel and Dacarbazine with filgrastim administration in advanced malignant melanoma 2002 Cancer Investigation 20 3 357-361

77. Freeman-Keller, M.; Kim, Y.; Cronin, H.; Richards, A.; Gibney, G.; Weber, J. S. Nivolumab in resected and unresectable metastatic melanoma: Characteristics of immune-related adverse events and association with outcomes 2016 Clinical Cancer Research 22 4 886-894

78. Geukes Foppen, M. H.; Brandsma, D.; Blank, C. U.; van Thienen, J. V.; Haanen, J. B.; Boogerd, W. Targeted treatment and immunotherapy in leptomeningeal metastases from melanoma 2016 Annals of Oncology 27 6 1138-1142

79. Gogas, H.; Ioannovich, J.; Dafni, U.; Stavropoulou-Giokas, C.; Frangia, K.; Tsoutsos, D.; Panagiotou, P.; Polyzos, A.; Papadopoulos, O.; Stratigos, A.; Markopoulos, C.; Bafaloukos, D.; Pectasides, D.; Fountzilas, G.; Kirkwood, J. M. Prognostic significance of autoimmunity during treatment of melanoma with interferon 2006 New England Journal of Medicine 354 7 709-718

80. Gorbonova, V. A.; Egorov, G. N.; Perevodchikova, N. I.; Orel, N. F. Combined chemotherapy with or without interferon alpha N1 (IFN) for advanced malignant melanoma--a randomized pilot phase III study 2000 Gan to kagaku ryoho Cancer & chemotherapy. 27 Suppl 2 310-314

81. Gray, E. S.; Reid, A. L.; Bowyer, S.; Calapre, L.; Siew, K.; Pearce, R.; Cowell, L.; Frank, M. H.; Millward, M.; Ziman, M. Circulating Melanoma Cell Subpopulations: Their Heterogeneity and Differential Responses to Treatment 2015 Journal of Investigative Dermatology 135 8 2040-2048

82. Grob, J. J.; Jouary, T.; Dreno, B.; Asselineau, J.; Gutzmer, R.; Hauschild, A.; Leccia, M. T.; Landthaler, M.; Garbe, C.; Sassolas, B.; Herbst, R. A.; Guillot, B.; Chene, G.; Pehamberger, H. Adjuvant therapy with pegylated interferon alfa-2b (36 months) versus low-dose interferon alfa-2b (18 months) in melanoma patients without macrometastatic nodes: An open-label, randomised, phase 3 European Association for Dermato-Oncology (EADO) study 2013 European Journal of Cancer 49 1 166-174

83. Grob, J.; Hamid, O.; Wolchok, J.; Maio, M.; Neyns, B.; Thomas, L.; De Pril, V.; Ibrahim, R.; O'Day, S.; Lebbe, C. Antitumor responses to ipilimumab in advanced melanoma are not affected by systemic corticosteroids used to manage immune-related adverse events (irAEs) 2009 European Journal of Cancer, Supplement 7 (2-3) 580

84. Gutzmer, R.; Koop, A.; Meier, F.; Hassel, J. C.; Terheyden, P.; Zimmer, L.; Heinzerling, L.; Ugurel, S.; Pfohler, C.; Gesierich, A.; Livingstone, E.; Satzger, I.; Kahler, K. C. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity 2017 European Journal of Cancer 75 24-32

85. Hamid, O.; Chasalow, S. D.; Tsuchihashi, Z.; Alaparthy, S.; Galbraith, S.; Berman, D. Association of baseline and on-study tumor biopsy markers with clinical activity in patients (pts) with advanced melanoma treated with ipilimumab 2009 Journal of Clinical Oncology 1) 9008

86. Hamid, O.; Chin, K.; Li, J.; Neyns, B.; Linette, G.; Negrier, S.; Lutzky, J.; Hoos, A.; Wolchock, J.; Lebbe, C. Dose effect of ipilimumab in patients with advanced melanoma: Results from a phase II, randomized, dose-ranging study 2008 Journal of Clinical Oncology 26 15_suppl 9025

87. Han, C.; Braybrooke, J. P.; Deplanque, G.; Taylor, M.; Mackintosh, D.; Kaur, K.; Samouri, K.; Ganesan, T. S.; Harris, A. L.; Talbot, D. C. Comparison of prognostic factors in patients in phase I trials of cytotoxic drugs vs new noncytotoxic agents 2003 British Journal of Cancer 89 7 1166-1171

88. Heinzerling, L. M.; Anliker, M. D.; Muller, J.; Schlaeppi, M.; Von Moos, R. Sarcoidosis induced by interferon-alpha in melanoma patients: Incidence, clinical manifestations, and management strategies 2010 Journal of Immunotherapy 33 8 834-839

89. Hida, T.; Yoneta, A.; Wakamatsu, K.; Yanagisawa, K.; Ishii-Osai, Y.; Kan, Y.; Kato, J.; Yamashita, T. Circulating melanoma cells as a potential biomarker to detect metastasis and evaluate prognosis 2016 Australasian Journal of Dermatology 57 2 145-149

90. Hodi, F. S.; O'Day, S. J.; McDermott, D. F.; Weber, R. W.; Sosman, J. A.; Haanen, J. B.; Gonzalez, R.; Robert, C.; Schadendorf, D.; Hassel, J. C.; Akerley, W.; van den Eertwegh, A. J.; Lutzky, J.; Lorigan, P.; Vaubel, J. M.; Linette, G. P.; Hogg, D.; Ottensmeier, C. H.; Lebbe, C.; Peschel, C.; Quirt, I.; Clark, J. I.; Wolchok, J. D.; Weber, J. S.; Tian, J.; Yellin, M. J.; Nichol, G. M.; Hoos, A.; Urba, W. J. Improved survival with ipilimumab in patients with metastatic melanoma.[Erratum appears in N Engl J Med. 2010 Sep 23;363(13):1290] 2010 New England Journal of Medicine 363 8 711-23

91. Hurabielle, C.; Pillebout, E.; Stehle, T.; Pages, C.; Roux, J.; Schneider, P.; Chevret, S.; Chaffaut, C.; Boutten, A.; Mourah, S.; Basset-Seguin, N.; Vidal-Petiot, E.; Lebbe, C.; Flamant, M. Mechanisms Underpinning Increased Plasma Creatinine Levels in Patients Receiving Vemurafenib for Advanced Melanoma 2016 PLoS ONE [Electronic Resource] 11 3 e0149873

92. Infante, J. R.; Fecher, L. A.; Falchook, G. S.; Nallapareddy, S.; Gordon, M. S.; Becerra, C.; DeMarini, D. J.; Cox, D. S.; Xu, Y.; Morris, S. R.; Peddareddigari, V. G. R.; Le, N. T.; Hart, L.; Bendell, J. C.; Eckhardt, G.; Kurzrock, R.; Flaherty, K.; Burris, H. A.; Messersmith, W. A. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: A phase 1 dose-escalation trial 2012 The Lancet Oncology 13 8 773-781

93. Iqbal, S.; Lenz, H. J.; Gandara, D. R.; Shibata, S. I.; Groshen, S.; Synold, T. W.; Newman, E. M. A phase i trial of oxaliplatin in combination with docetaxel in patients with advanced solid tumors 2013 Cancer Chemotherapy and Pharmacology 72 1 85-91

94. Jacquelot, N.; Enot, D. P.; Flament, C.; Vimond, N.; Blattner, C.; Pitt, J. M.; Yamazaki, T.; Roberti, M. P.; Daillere, R.; Vetizou, M.; Poirier-Colame, V.; Semeraro, M.; Caignard, A.; Slingluff, C. L., Jr.; Sallusto, F.; Rusakiewicz, S.; Weide, B.; Marabelle, A.; Kohrt, H.; Dalle, S.; Cavalcanti, A.; Kroemer, G.; Di Giacomo, A. M.; Maio, M.; Wong, P.; Yuan, J.; Wolchok, J.; Umansky, V.; Eggermont, A.; Zitvogel, L. Chemokine receptor patterns in lymphocytes mirror metastatic spreading in melanoma 2016 Journal of Clinical Investigation 126 3 921-37

95. Janinis, J.; Kapelari, K.; Efstathiou, E.; Pectasides, D.; Tsavaris, N.; Skarlos, D. A pilot study of temozolomide as first line therapy of central nervous system metastases from malignant melanoma 2000 Journal of B.U.ON. 5 3 277-280

96. Jiang, L.; Lv, X.; Li, J.; Li, X.; Li, W.; Li, Y. The status of microRNA-21 expression and its clinical significance in human cutaneous malignant melanoma 2012 Acta Histochemica 114 6 582-588

97. Johnson, A. G.; Ruiz, J.; Hughes, R.; Brandi, R. Page; Isom, S.; Lucas, J. T.; McTyre, E. R.; Houseknecht, K. W.; Ayala-Peacock, D. N.; Bourland, D. J.; Hinson, W. H.; Laxton, A. W.; Tatter, S. B.; Debinski, W.; Watabe, K.; Chan, M. D. Impact of systemic targeted agents on the clinical outcomes of patients with brain metastases 2015 Oncotarget 6 22 18945-18955

98. Jonasch, E.; Kumar, U. N.; Linette, G. P.; Hodi, F. S.; Soiffer, R. J.; Ryan, B. F.; Sober, A. J.; Mihm, M. C.; Tsao, H.; Langley, R. G.; Cosimi, B. A.; Gadd, M. A.; Tanabe, K. K.; Souba, W.; Haynes, H. A.; Barnhill, R.; Osteen, R.; Haluska, F. G. Adjuvant high-dose interferon alfa-2b in patients with high-risk melanoma 2000 Cancer Journal 6 3 139-45

99. Kandolf-Sekulovic, L.; Babovic, N.; Jokic, N.; Nikolin, B.; Nikolic, D.; Janjic, Z.; Mijugkovic, Z.; Rajovic, M.; Novakovic, M.; Pejcic, I.; Kovaevic, P.; Mihajlovic, D.; Roganovic, T.; Ferenc, V.; Nikolic, J.; Marinkovic, M.; Bizetic, Z. Clinicopathological characteristics, diagnosis and treatment of melanoma in Serbia--the Melanoma Focus Study 2015 Vojnosanitetski Pregled 72 4 312-6

100. Kanz, B. A.; Pollack, M. H.; Johnpulle, R.; Puzanov, I.; Horn, L.; Morgans, A.; Sosman, J. A.; Rapisuwon, S.; Conry, R. M.; Eroglu, Z.; Johnson, D. B. Safety and efficacy of anti-PD-1 in patients with baseline cardiac, renal, or hepatic dysfunction 2016 Journal for ImmunoTherapy of Cancer 4 (1) (no pagination) 60

101. Khoja, L.; Lorigan, P.; Zhou, C.; Lancashire, M.; Booth, J.; Cummings, J.; Califano, R.; Clack, G.; Hughes, A.; Dive, C. Biomarker utility of circulating tumor cells in metastatic cutaneous melanoma 2013 Journal of Investigative Dermatology 133 6 1582-1590

102. King, D. M.; Albertini, M. R.; Schalch, H.; Hank, J. A.; Gan, J.; Surfus, J.; Mahvi, D.; Schiller, J. H.; Warner, T.; Kim, K.; Eickhoff, J.; Kendra, K.; Reisfeld, R.; Gillies, S. D.; Sondel, P. Phase I clinical trial of the immunocytokine EMD 273063 in melanoma patients 2004 Journal of Clinical Oncology 22 22 4463-4473

103. Kirkwood, J. M.; Richards, T.; Zarour, H. M.; Sosman, J.; Ernstoff, M.; Whiteside, T. L.; Ibrahim, J.; Blum, R.; Wieand, S.; Mascari, R. Immunomodulatory effects of high-dose and low-dose interferon alpha2b in patients with high-risk resected melanoma: The E2690 Laboratory Corollary of Intergroup Adjuvant Trial E1690 2002 Cancer 95 5 1101-1112

104. Klein, O.; Clements, A.; Menzies, A. M.; O'Toole, S.; Kefford, R. F.; Long, G. V. BRAF inhibitor activity in V600R metastatic melanoma 2013 European Journal of Cancer 49 5 1073-1079

105. Kluger, H. M.; Zito, C. R.; Barr, M. L.; Baine, M. K.; Chiang, V. L. S.; Sznol, M.; Rimm, D. L.; Chen, L.; Jilaveanu, L. B. Characterization of PD-L1 expression and associated T-cell infiltrates in metastatic melanoma samples from variable anatomic sites 2015 Clinical Cancer Research 21 13 3052-3060

106. Koguchi, Y.; Hoen, H. M.; Bambina, S. A.; Rynning, M. D.; Fuerstenberg, R. K.; Curti, B. D.; Urba, W. J.; Milburn, C.; Bahjat, F. R.; Korman, A. J.; Bahjat, K. S. Serum Immunoregulatory Proteins as Predictors of Overall Survival of Metastatic Melanoma Patients Treated with Ipilimumab 2015 Cancer Research 75 23 5084-5092

107. Kottschade, L. A.; Suman, V. J.; Amatruda, Iii T.; McWilliams, R. R.; Mattar, B. I.; Nikcevich, D. A.; Behrens, R.; Fitch, T. R.; Jaslowski, A. J.; Markovic, S. N. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage IV melanoma 2011 Cancer 117 8 1704-10

108. Koyanagi, K.; O'Day, S. J.; Gonzalez, R.; Lewis, K.; Robinson, W. A.; Amatruda, T. T.; Kuo, C.; Wang, H. J.; Milford, R.; Morton, D. L.; Hoon, D. S. B. Microphthalmia transcription factor as a molecular marker for circulating tumor cell detection in blood of melanoma patients 2006 Clinical Cancer Research 12 4 1137-1143

109. Koyanagi, K.; O'Day, S. J.; Gonzalez, R.; Lewis, K.; Robinson, W. A.; Amatruda, T. T.; Wang, H. J.; Elashoff, R. M.; Takeuchi, H.; Umetani, N.; Hoon, D. S. Serial monitoring of circulating melanoma cells during neoadjuvant biochemotherapy for stage III melanoma: outcome prediction in a multicenter trial 2005 Journal of clinical oncology : official journal of the American Society of Clinical Oncology 23 31 8057-8064

110. Ladanyi, A.; Somlai, B.; Gilde, K.; Fejos, Z.; Gaudi, I.; Timar, J. T-Cell Activation Marker Expression on Tumor-Infiltrating Lymphocytes As Prognostic Factor in Cutaneous Malignant Melanoma 2004 Clinical Cancer Research 10 2 521-530

111. Larkin, J.; Hatswell, A. J.; Nathan, P.; Lebmeier, M.; Lee, D. The Predicted Impact of Ipilimumab Usage on Survival in Previously Treated Advanced or Metastatic Melanoma in the UK 2015 PLoS ONE [Electronic Resource] 10 12 e0145524

112. Lebbe, C.; How-Kit, A.; Battistella, M.; Sadoux, A.; Podgorniak, M. P.; Sidina, I.; Pages, C.; Roux, J.; Porcher, R.; Tost, J.; Mourah, S. BRAFV600 mutation levels predict response to vemurafenib in metastatic melanoma 2014 Fundamental and Clinical Pharmacology 28 96

113. Lonser, R. R.; Song, D. K.; Klapper, J.; Hagan, M.; Auh, S.; Kerr, P. B.; Citrin, D. E.; Heiss, J. D.; Camphausen, K.; Rosenberg, S. A. Surgical management of melanoma brain metastases in patients treated with immunotherapy: Clinical article 2011 Journal of Neurosurgery 115 1 30-36

114. Lorigan, P.; Marples, M.; Harries, M.; Wagstaff, J.; Dalgleish, A. G.; Osborne, R.; Maraveyas, A.; Nicholson, S.; Davidson, N.; Wang, Q.; Pericleous, L.; Bapat, U.; Middleton, M. R. Treatment patterns, outcomes, and resource utilization of patients with metastatic melanoma in the U.K.: The MELODY study 2014 British Journal of Dermatology 170 1 87-95

115. Lutzky, J.; Wolchok, J.; Hamid, O.; Lebbe, C.; Pehamberger, H.; Linette, G.; De Pril, V.; Ibrahim, R.; Hoos, A.; O'Day, S. Association between immune-related adverse events (irAEs) and disease control or overall survival in patients (pts) with advanced melanoma treated with 10 mg/kg ipilimumab in three phase II clinical trials 2009 Journal of Clinical Oncology 1) 9034

116. Ly, D.; Bagshaw, H. P.; Anker, C. J.; Tward, J. D.; Grossmann, K. F.; Jensen, R. L.; Shrieve, D. C. Local control after stereotactic radiosurgery for brain metastases in patients with melanoma with and without BRAF mutation and treatment 2015 Journal of Neurosurgery 123 2 395-401

117. Maccalli, C.; Giannarelli, D.; Capocefalo, F.; Pilla, L.; Fonsatti, E.; Di Giacomo, A. M.; Parmiani, G.; Maio, M. Immunological markers and clinical outcome of advanced melanoma patients receiving ipilimumab plus fotemustine in the NIBIT-M1 study 2016 OncoImmunology 5 2

118. Margolin, K.; Atkins, M. B.; Dutcher, J. P.; Ernstoff, M. S.; Smith, Ii J. W.; Clark, J. I.; Baar, J.; Sosman, J.; Weber, J.; Lathia, C.; Brunetti, J.; Cihon, F.; Schwartz, B. Phase I trial of BAY 50-4798, an interleukin-2-specific agonist in advanced melanoma and renal cancer 2007 Clinical Cancer Research 13 11 3312-3319

119. Markovic, S. N.; Suman, V. J.; Kottschade, L. A.; Amatruda, T.; McWilliams, R. R.; Dakhil, S. R.; Nikcevich, D. A.; Morton, R. F.; Fitch, T. R.; Jaslowski, A. J. A phase II trial of carboplatin (C) and nab-paclitaxel (ABI-007-nab-P) in patients with unresectable stage IV melanoma: Final data from N057E 2009 Journal of Clinical Oncology 1) 9055

120. Markulin Grgic, L.; Nishliu, M.; Santek, F.; Rakusic, Z.; Kukura, V.; Podolski, P.; Stepanic, V.; Tvrdeic Santek, M.; Budisic, Z.; Erak, V. The role of prognostic factors on survival of patients with brain metastases 2004 Neurologia Croatica 53 3-4 61-68

121. Marroquin, C. E.; White, D. E.; Steinberg, S. M.; Rosenberg, S. A.; Schwartzentruber, D. J. Decreased tolerance to interleukin-2 with repeated courses of therapy in patients with metastatic melanoma or renal cell cancer 2000 Journal of Immunotherapy 23 3 387-392

122. Masci, P.; Olencki, T.; Wood, L.; Rybicki, L.; Jacobs, B.; Williams, B.; Faber, P.; Bukowski, R.; Tong, K.; Borden, E. C. Gene modulatory effects, pharmacokinetics, and clinical tolerance of interferon-alpha1b: A second member of the interferon-alpha family 2007 Clinical Pharmacology and Therapeutics 81 3 354-361

123. Massi, D.; Brusa, D.; Merelli, B.; Ciano, M.; Audrito, V.; Serra, S.; Buonincontri, R.; Baroni, G.; Nassini, R.; Minocci, D.; Cattaneo, L.; Tamborini, E.; Carobbio, A.; Rulli, E.; Deaglio, S.; Mandala, M. PD-L1 marks a subset of melanomas with a shorter overall survival and distinct genetic and morphological characteristics 2014 Annals of Oncology 25 12 2433-2442

124. McArthur, G. A.; Puzanov, I.; Amaravadi, R.; Ribas, A.; Chapman, P.; Kim, K. B.; Sosman, J. A.; Lee, R. J.; Nolop, K.; Flaherty, K. T.; Callahan, J.; Hicks, R. J. Marked, homogeneous, and early [¹⁸F]fluorodeoxyglucose-positron emission tomography responses to vemurafenib in BRAF-mutant advanced melanoma 2012 Journal of Clinical Oncology 30 14 1628-1634

125. McMasters, K. M.; Edwards, M. J.; Ross, M. I.; Reintgen, D. S.; Martin, R. C., 2nd; Urist, M. M.; Noyes, R. D.; Sussman, J. J.; Stromberg, A. J.; Scoggins, C. R. Ulceration as a predictive marker for response to adjuvant interferon therapy in melanoma 2010 Annals of Surgery 252 3 460-5; discussion 465-6

126. McQuade, J. L.; Posada, L. P.; Lecagoonporn, S.; Cain, S.; Bassett, R. L.; Patel, S. P.; Hwu, W. J.; Hwu, P.; Davies, M. A.; Bedikian, A. Y.; Amaria, R. N. A phase I study of TPI 287 in combination with temozolomide for patients with metastatic melanoma 2016 Melanoma Research 26 6 604-608

127. Meral, R.; Duranyildiz, D.; Tas, F.; Camlica, H.; Yasasever, V.; Kurul, S.; Dalay, N. Prognostic significance of melanoma inhibiting activity levels in malignant melanoma 2001 Melanoma Research 11 6 627-632

128. Meyer, S.; Wild, P. J.; Vogt, T.; Bataille, F.; Ehret, C.; Gantner, S.; Landthaler, M.; Klinkhammer-Schalke, M.; Hofstaedter, F.; Bosserhoff, A. K. Methylthioadenosine phosphorylase represents a predictive marker for response to adjuvant interferon therapy in patients with malignant melanoma 2010 Experimental Dermatology 19 8 e251-e257

129. Middleton, M. R.; Grob, J. J.; Aaronson, N.; Fierlbeck, G.; Tilgen, W.; Seiter, S.; Gore, M.; Aamdal, S.; Cebon, J.; Coates, A.; Dreno, B.; Henz, M.; Schadendorf, D.; Kapp, A.; Weiss, J.; Fraass, U.;

Statkevich, P.; Muller, M.; Thatcher, N. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma.[Erratum appears in J Clin Oncol 2000 Jun;18(11):2351] 2000 Journal of Clinical Oncology 18 1 158-66

130. Minor, D. R.; Moore, D.; Kim, C.; Kashani-Sabet, M.; Venna, S. S.; Wang, W.; Boasberg, P.; O'Day, S. Prognostic factors in metastatic melanoma patients treated with biochemotherapy and maintenance immunotherapy 2009 Oncologist 14 10 995-1002

131. Mita, C.; Chatelut, E.; Bekradda, M.; Soulie, P.; Canal, P.; Misset, J. L.; Cvitkovic, E.; Bugat, R. Phase I and pharmacological study of an oxaliplatin and carboplatin combination in advanced malignancies 2003 Annals of Oncology 14 12 1776-1782

132. Mori, T.; O'Day, S. J.; Umetani, N.; Martinez, S. R.; Kitago, M.; Koyanagi, K.; Kuo, C.; Takeshima, T. L.; Milford, R.; Wang, H. J.; Vu, V. D.; Nguyen, S. L.; Hoon, D. S. Predictive utility of circulating methylated DNA in serum of melanoma patients receiving biochemotherapy 2005 Journal of clinical oncology : official journal of the American Society of Clinical Oncology 23 36 9351-9358

133. Moschos, S. J.; Edington, H. D.; Land, S. R.; Rao, U. N.; Jukic, D.; Shipe-Spotloe, J.; Kirkwood, J. M. Neoadjuvant treatment of regional stage IIIB melanoma with high-dose interferon alfa-2b induces objective tumor regression in association with modulation of tumor infiltrating host cellular immune responses 2006 Journal of Clinical Oncology 24 19 3164-3171

134. Mouawad, R.; Spano, J. P.; Comperat, E.; Capron, F.; Khayat, D. Tumoural expression and circulating level of VEGFR-3 (Flt-4) in metastatic melanoma patients: Correlation with clinical parameters and outcome 2009 European Journal of Cancer 45 8 1407-1414

135. Movva, S.; Verschraegen, C. F.; Rabinowitz, I.; Mangalik, A.; Parks, V.; Lee, F. C. Phase I dose finding study of carboplatin, paclitaxel, and temozolomide in advanced solid tumors 2011 Melanoma Research 21 1 76-79

136. Najjar, Y. G.; Ding, F.; Lin, Y.; VanderWeele, R.; Butterfield, L. H.; Tarhini, A. A. Melanoma antigen-specific effector T cell cytokine secretion patterns in patients treated with ipilimumab 2017 Journal of Translational Medicine 15 (1) (no pagination) 39

137. Nardin, A.; Wong, W. C.; Tow, C.; Molina, T. J.; Tissier, F.; Audebourg, A.; Garcette, M.; Caignard, A.; Avril, M. F.; Abastado, J. P.; Prevost-Blondel, A. Dacarbazine promotes stromal remodeling and lymphocyte infiltration in cutaneous melanoma lesions 2011 Journal of Investigative Dermatology 131 9 1896-1905

138. Neagu, M.; Constantin, C.; Surcel, M.; Zurac, S. Cytokine/chemokine pattern in cutaneous melanoma 2016 European Journal of Immunology 46 221-222

139. Nikkola, J.; Vihinen, P.; Vlaykova, T.; Hahka-Kemppinen, M.; Kahari, V. M.; Pyrhonen, S. High expression levels of collagenase-1 and stromelysin-1 correlate with shorter disease-free survival in human metastatic melanoma 2002 International Journal of Cancer 97 4 432-8

140. O'Day, S. J.; Boasberg, P. D.; Piro, L.; Kristedja, T. S.; Wang, H. J.; Martin, M.; Deck, R.; Ames, P.; Shinn, K.; Kim, H.; Fournier, P.; Gammon, G. Maintenance biotherapy for metastatic melanoma with interleukin-2 and Granulocyte macrophage-colony stimulating factor improves survival for patients responding to induction concurrent biochemotherapy 2002 Clinical Cancer Research 8 9 2775-2781

141. Ohno, R.; Yamaguchi, Y.; Toge, T.; Kinouchi, T.; Kotake, T.; Shibata, M.; Kiyohara, Y.; Ikeda, S.; Fukui, I.; Gohchi, A.; Sugiyama, Y.; Saji, S.; Hazama, S.; Oka, M.; Ohnishi, K.; Ohhashi, Y.; Tsukagoshi, S.; Taguchi, T. A dose-escalation and pharmacokinetic study of subcutaneously administered recombinant human interleukin 12 and its biological effects in Japanese patients with advanced malignancies 2000 Clinical Cancer Research 6 7 2661-2669

142. Patnaik, A.; Kang, S. P.; Rasco, D.; Papadopoulos, K. P.; Elassaiss-Schaap, J.; Beeram, M.; Drengler, R.; Chen, C.; Smith, L.; Espino, G.; Gergich, K.; Delgado, L.; Daud, A.; Lindia, J. A.; Li, X. N.; Pierce, R. H.; Yearley, J. H.; Wu, D.; Laterza, O.; Lehnert, M.; Iannone, R.; Tolcher, A. W. Phase I Study of Pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors 2015 Clinical Cancer Research 21 19 4286-93

143. Petrella, T. M.; Tozer, R.; Belanger, K.; Savage, K. J.; Wong, R.; Smylie, M.; Kamel-Reid, S.; Tron, V.; Chen, B. E.; Hunder, N. N.; Hagerman, L.; Walsh, W.; Eisenhauer, E. A. Interleukin-21 has activity in patients with metastatic melanoma: a phase II study 2012 Journal of Clinical Oncology 30 27 3396-401

144. Powderly, J. D.; O'Day, S. J.; Hersh, E. M.; Tchekmedyian, S.; Hodi, F. S.; Nichol, G.; Yellin, M. J.; Urba, W. J.; Samlowski, W. E.; Weber, J. S. Prolonged survival in objective responders to ipilimumab therapy 2008 Journal of Clinical Oncology 26 15_suppl 20004

145. Puzanov, I. Braf-validated target in metastatic melanoma 2010 Current Treatment Options in Oncology 11 71-74

146. Quaglino, P.; Marenco, F.; Osella-Abate, S.; Cappello, N.; Ortoncelli, M.; Salomone, B.; Fierro, M. T.; Savoia, P.; Bernengo, M. G. Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: Results from a single-institution hospital-based observational cohort study 2010 Annals of Oncology 21 2 409-414

147. Quan Jr, W. D. Y.; Khan, N.; Ramirez, M.; Taylor, W. C.; Quan, F.; Vinogradov, M.; Walker, P. Correlation between development of pulmonary edema and response of pulmonary metastases of metastatic melanoma and kidney cancer to high-dose continuous-infusion interleukin-2 2005 Cancer Biotherapy and Radiopharmaceuticals 20 2 151-154

148. Queirolo, P.; Simeone, E.; De Galitiis, F.; Di Guardo, L.; Di Giacomo, A. M.; Marconcini, R.; Ferraresi, V.; De Rosa, F.; Guida, M.; Stragliotto, S. Efficacy and safety data from patients with advanced melanoma and brain metastases participating in the european ipilimumab expanded access programme (EAP) in Italy 2012 Annals of Oncology 23 28

149. Ray, A.; Williams, M. A.; Meek, S. M.; Bowen, R. C.; Grossmann, K. F.; Andtbacka, R. H. I.; Bowles, T. L.; Hyngstrom, J. R.; Leachman, S. A.; Grossman, D.; Bowen, G. M.; Holmen, S. L.; VanBrocklin, M. W.; Suneja, G.; Khong, H. T. A phase I study of intratumoral ipilimumab and interleukin-2 in patients with advanced melanoma 2016 Oncotarget 7 39 64390-64399

150. Retseck, J.; VanderWeele, R.; Lin, H. M.; Lin, Y.; Butterfield, L. H.; Tarhini, A. A. Phenotypic and functional testing of circulating regulatory T cells in advanced melanoma patients treated with neoadjuvant ipilimumab 2016 Journal for ImmunoTherapy of Cancer 4 (1) (no pagination) 38

151. Riker, A. I.; Rossi, G. R.; Masih, P.; Alsfeld, L. C.; Denham, F.; Tennant, L.; Ramsey, W. J.; Vahanian, N. N.; Link, C. J. Combination immunotherapy for high-risk resected and metastatic melanoma patients 2014 Ochsner Journal 14 2 164-174

152. Robert, C.; Schadendorf, D.; Messina, M.; Hodi, F. S.; O'Day, S. Efficacy and safety of retreatment with ipilimumab in patients with pretreated advanced melanoma who progressed after initially achieving disease control 2013 Clinical Cancer Research 19 8 2232-2239

153. Rochlitz, C.; Dreno, B.; Jantscheff, P.; Cavalli, F.; Squiban, P.; Acres, B.; Baudin, M.; Escudier, B.; Heinzerling, L.; Morant, R.; Herrmann, R.; Dietrich, P. Y.; Dummer, R. Immunotherapy of metastatic melanoma by intratumoral injections of Vero cells producing human IL-2: Phase II randomized study comparing two dose levels 2002 Cancer Gene Therapy 9 3 289-295

154. Roh, W.; Chen, P. L.; Reuben, A.; Spencer, C. N.; Prieto, P. A.; Miller, J. P.; Gopalakrishnan, V.; Wang, F.; Cooper, Z. A.; Reddy, S. M.; Gumbs, C.; Little, L.; Chang, Q.; Chen, W. S.; Wani, K.; De Macedo, M. P.; Chen, E.; Austin-Breneman, J. L.; Jiang, H.; Roszik, J.; Tetzlaff, M. T.; Davies, M. A.; Gershenwald, J. E.; Tawbi, H.; Lazar, A. J.; Hwu, P.; Hwu, W. J.; Diab, A.; Glitza, I. C.; Patel, S. P.; Woodman, S. E.; Amaria, R. N.; Prieto, V. G.; Hu, J.; Sharma, P.; Allison, J. P.; Chin, L.; Zhang, J.; Wargo, J. A.; Futreal, P. A. Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance 2017 Science Translational Medicine 9 (379) (no pagination) eaah3560

155. Rosen, L. S.; LoRusso, P.; Ma, W. W.; Goldman, J. W.; Weise, A.; Colevas, A. D.; Adjei, A.; Yazji, S.; Shen, A.; Johnston, S.; Hsieh, H. J.; Chan, I. T.; Sikic, B. I. A first-in-human phase I study to evaluate the MEK1/2 inhibitor, cobimetinib, administered daily in patients with advanced solid tumors 2016 Investigational New Drugs 34 5 604-613

156. Rossi, C. R.; Lejeune, F. J.; Pontes, L.; Foletto, M.; De Salvo, G. L.; Pilati, P. L.; Mocellin, S.; Ribeiro, M.; Lopes, M.; Lise, M. Phase I-II study on isolation antiblastic fotemustine perfusion after

dacarbazine chemosensitization for advanced melanoma of the extremities 2003 Melanoma Research 13 3 293-297

157. Schmidt, H.; Bastholt, L.; Geertsen, P.; Christensen, I. J.; Larsen, S.; Gehl, J.; Von Der Maase, H. Elevated neutrophil and monocyte counts in peripheral blood are associated with poor survival in patients with metastatic melanoma: A prognostic model 2005 British Journal of Cancer 93 3 273-278

158. Shahabi, V.; Berman, D.; Chasalow, S. D.; Wang, L.; Tsuchihashi, Z.; Hu, B.; Panting, L.; Jure-Kunkel, M.; Ji, R. R. Gene expression profiling of whole blood in ipilimumab-treated patients for identification of potential biomarkers of immune-related gastrointestinal adverse events 2013 Journal of Translational Medicine 11 (1) (no pagination) 75

159. Shimizu, T.; Seto, T.; Hirai, F.; Takenoyama, M.; Nosaki, K.; Tsurutani, J.; Kaneda, H.; Iwasa, T.; Kawakami, H.; Noguchi, K.; Shimamoto, T.; Nakagawa, K. Phase 1 study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in Japanese patients with advanced solid tumors 2016 Investigational New Drugs 34 3 347-354

160. Sloot, S.; Zager, J. S.; Kudchadkar, R. R.; Messina, J. L.; Benedict, J. J.; Gonzalez, R. J.; DeConti, R.; Turner, L. M.; McCardle, T.; Smalley, K. S.; Weber, J. S.; Sondak, V. K.; Gibney, G. T. BRAF inhibition for advanced locoregional BRAF V600E mutant melanoma: a potential neoadjuvant strategy 2016 Melanoma Research 26 1 83-7

161. Smit, L. H. M.; Nieweg, O. E.; Mooi, W. J.; Bonfrer, J. M. G.; Haanen, J. B. A. G.; Kroon, B. B. R.; De Gast, G. C. Value of serum S-100B for prediction of distant relapse and survival in stage III B/C melanoma 2008 Anticancer Research 28 4 C 2297-2302

162. Smith, Ii Jw; Kurt, R. A.; Baher, A. G.; Denman, S.; Justice, L.; Doran, T.; Gilbert, M.; Alvord, W. G.; Urba, W. J. Immune effects of escalating doses of granulocyte-macrophage colony-stimulating factor added to a fixed, low-dose, inpatient interleukin-2 regimen: a randomized phase I trial in patients with metastatic melanoma and renal cell carcinoma 2003 Journal of Immunotherapy 26 2 130-8

163. Spanknebel, K.; Cheung, K. Y.; Stoutenburg, J.; Hurst-Wicker, K.; Hesdorffer, C.; DeRaffele, G.; Kaufman, H. L. Initial clinical response predicts outcome and is associated with dose schedule in metastatic melanoma and renal cell carcinoma patients treated with high-dose interleukin 2 2005 Annals of Surgical Oncology 12 5 1-10

164. Strannegard, O.; Thoren, F. B. Opposing effects of immunotherapy in melanoma using multisubtype interferon-alpha - can tumor immune escape after immunotherapy accelerate disease progression? 2016 OncoImmunology 5 3

165. Strobel, K.; Dummer, R.; Steinert, H. C.; Conzett, K. B.; Schad, K.; Lago, M. P.; Soyka, J. D.; Veit-Haibach, P.; Seifert, B.; Kalff, V. Chemotherapy response assessment in stage IV melanoma patients

- Comparison of ¹⁸F-FDG-PET/CT, CT, brain MRI, and tumormarker S-100B 2008 European Journal of Nuclear Medicine and Molecular Imaging 35 10 1786-1795

166. Tallerico, R.; Cristiani, C. M.; Staaf, E.; Garofalo, C.; Sottile, R.; Capone, M.; Pico de Coana, Y.; Madonna, G.; Palella, E.; Wolodarski, M.; Carannante, V.; Mallardo, D.; Simeone, E.; Grimaldi, A. M.; Johansson, S.; Frumento, P.; Gulletta, E.; Anichini, A.; Colucci, F.; Ciliberto, G.; Kiessling, R.; Karre, K.; Ascierto, P. A.; Carbone, E. IL-15, TIM-3 and NK cells subsets predict responsiveness to anti-CTLA-4 treatment in melanoma patients 2017 OncoImmunology 6 (2) (no pagination) e1261242

167. Tarhini, A. A.; Kirkwood, J. M.; Gooding, W. E.; Moschos, S.; Agarwala, S. s Erratum: A phase 2 trial of sequential temozolomide chemotherapy followed by high-dose interleukin 2immunotherapy for metastatic melanoma (Cancer (2008) 113 (1632-40)) 2013 Cancer 119 4 924

168. Tarhini, A. A.; Kirkwood, J. M.; Gooding, W. E.; Moschos, S.; Agarwala, S. S. A phase 2 trial of sequential temozolomide chemotherapy followed by high-dose interleukin 2 immunotherapy for metastatic melanoma.[Erratum appears in Cancer. 2013 Feb 15;119(4):924] 2008 Cancer 113 7 1632-40

169. Tarhini, A.; Agarwala, S. S.; Gooding, W.; Cai, C.; Kirkwood, J. M.; Stover, L. L.; Blair, H. Phase II trial of sequential temozolomide (TMZ) and high-dose bolus (HDB) IL-2 in patients with AJCC stage IV melanoma 2005 Journal of Clinical Oncology 23 16_suppl 7549

170. Tas, F.; Kurul, S.; Camlica, H.; Topuz, E. Malignant melanoma in Turkey: A single institution's experience on 475 cases 2006 Japanese Journal of Clinical Oncology 36 12 794-799

171. Thompson, J. A.; Curti, B. D.; Redman, B. G.; Bhatia, S.; Weber, J. S.; Agarwala, S. S.; Sievers, E. L.; Hughes, S. D.; Devries, T. A.; Hausman, D. F. Phase I study of recombinant interleukin-21 in patients with metastatic melanoma and renal cell carcinoma 2008 Journal of Clinical Oncology 26 12 2034-2039

172. Tumeh, P. C.; Harview, C. L.; Yearley, J. H.; Shintaku, I. P.; Taylor, E. J.; Robert, L.; Chmielowski, B.; Spasic, M.; Henry, G.; Ciobanu, V.; West, A. N.; Carmona, M.; Kivork, C.; Seja, E.; Cherry, G.; Gutierrez, A. J.; Grogan, T. R.; Mateus, C.; Tomasic, G.; Glaspy, J. A.; Emerson, R. O.; Robins, H.; Pierce, R. H.; Elashoff, D. A.; Robert, C.; Ribas, A. PD-1 blockade induces responses by inhibiting adaptive immune resistance 2014 Nature 515 7528 568-71

173. Ugurel, S.; Houben, R.; Schrama, D.; Voigt, H.; Zapatka, M.; Schadendorf, D.; Brocker, E. B.; Becker, J. C. Microphthalmia-associated transcription factor gene amplification in metastatic melanoma is a prognostic marker for patient survival, but not a predictive marker for chemosensitivity and chemotherapy response 2007 Clinical Cancer Research 13 21 6344-6350

174. Ugurel, S.; Rappl, G.; Tilgen, W.; Reinhold, U. Increased soluble CD95 (sFas/CD95) serum level correlates with poor prognosis in melanoma patients 2001 Clinical Cancer Research 7 5 1282-1286

175. Ugurel, S.; Rappl, G.; Tilgen, W.; Reinhold, U. Increased serum concentration of angiogenic factors in malignant melanoma patients correlates with tumor progression and survival 2001 Journal of Clinical Oncology 19 2 577-583

176. Ugurel, S.; Rebmann, V.; Ferrone, S.; Tilgen, W.; Grosse-Wilde, H.; Reinhold, U. Soluble human leukocyte antigen-G serum level is elevated in melanoma patients and is further increased by interferon-alpha immunotherapy 2001 Cancer 92 2 369-376

177. Van Allen, E. M.; Miao, D.; Schilling, B.; Shukla, S. A.; Blank, C.; Zimmer, L.; Sucker, A.; Hillen, U.; Geukes Foppen, M. H.; Goldinger, S. M.; Utikal, J.; Hassel, J. C.; Weide, B.; Kaehler, K. C.; Loquai, C.; Mohr, P.; Gutzmer, R.; Dummer, R.; Gabriel, S.; Wu, C. J.; Schadendorf, D.; Garraway, L. A. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma.[Erratum appears in Science. 2015 Nov 13;350(6262):aad8366; PMID: 26564858], [Erratum appears in Science. 2016 Apr 15;352(6283). pii: aaf8264. doi: 10.1126/science.aaf8264; PMID: 27081077] 2015 Science 350 6257 207-11

178. Vandersleyen, V.; Grosber, M.; Wilgenhof, S.; De Kock, J.; Neyns, B.; Gutermuth, J. Vemurafenib-associated Dupuytren- and Ledderhose palmoplantar fibromatosis in metastatic melanoma patients 2016 Journal of the European Academy of Dermatology and Venereology 30 7 1133-1135

179. Vihinen, P.; Kallioinen, M.; Vuoristo, M. S.; Ivaska, J.; Syrjanen, K. J.; Hahka-Kemppinen, M.; Kellokumpu-Lehtinen, P. L.; Pyrhonen, S. O. Serum angiogenin levels predict treatment response in patients with stage IV melanoma 2007 Clinical and Experimental Metastasis 24 7 567-574

180. Villa, S.; Weber, D. C.; Moretones, C.; Manes, A.; Combescure, C.; Jove, J.; Puyalto, P.; Cuadras, P.; Bruna, J.; Verger, E.; Balana, C.; Graus, F. Validation of the new graded prognostic assessment scale for brain metastases: A multicenter prospective study 2011 Radiation Oncology 6 (1) (no pagination) 23

181. Voelter-Mahlknecht, S.; Mahlknecht, U.; Letzel, S.; Fierlbeck, G. Phase 2 trial of the continuous IV administration of interferon-beta in patients with disseminated malignant melanoma 2006 Skinmed 5 6 271-276

182. Von Hoff, D. D.; Mita, M. M.; Ramanathan, R. K.; Weiss, G. J.; Mita, A. C.; Lorusso, P. M.; Burris, H. A.; Hart, L. L.; Low, S. C.; Parsons, D. M.; Zale, S. E.; Summa, J. M.; Youssoufian, H.; Sachdev, J. C. Phase I study of PSMA-targeted docetaxel-containing nanoparticle BIND-014 in patients with advanced solid tumors 2016 Clinical Cancer Research 22 13 3157-3163

183. Vuoristo, M. S.; Laine, S.; Huhtala, H.; Parvinen, L. M.; Hahka-Kemppinen, M.; Korpela, M.; Kumpulainen, E.; Kellokumpu-Lehtinen, P. Serum adhesion molecules and interleukin-2 receptor as markers of tumour load and prognosis in advanced cutaneous melanoma 2001 European Journal of Cancer 37 13 1629-1634

184. Wang, W.; Edington, H. D.; Rao, U. N.; Jukic, D. M.; Land, S. R.; Ferrone, S.; Kirkwood, J. M. Modulation of signal transducers and activators of transcription 1 and 3 signaling in melanoma by high-dose IFNalpha2b 2007 Clinical Cancer Research 13 5 1523-31

185. Weide, B.; Martens, A.; Zelba, H.; Stutz, C.; Derhovanessian, E.; Di Giacomo, A. M.; Maio, M.; Sucker, A.; Schilling, B.; Schadendorf, D.; Buttner, P.; Garbe, C.; Pawelec, G. Myeloid-derived suppressor cells predict survival of patients with advanced melanoma: Comparison with regulatory T cells and NY-ESO-1- or melan-A-specific T cells 2014 Clinical Cancer Research 20 6 1601-1609

186. Weide, B.; Schafer, T.; Martens, A.; Kuzkina, A.; Uder, L.; Noor, S.; Garbe, C.; Harter, P. N.; Mittelbronn, M.; Wischhusen, J. High GDF-15 Serum Levels Independently Correlate with Poorer Overall Survival of Patients with Tumor-Free Stage III and Unresectable Stage IV Melanoma 2016 Journal of Investigative Dermatology 136 12 2444-2452

187. Wilmott, J. S.; Long, G. V.; Howle, J. R.; Haydu, L. E.; Sharma, R. N.; Thompson, J. F.; Kefford, R. F.; Hersey, P.; Scolyer, R. A. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma 2012 Clinical Cancer Research 18 5 1386-1394

188. Wilmott, J. S.; Menzies, A. M.; Haydu, L. E.; Capper, D.; Preusser, M.; Zhang, Y. E.; Thompson, J. F.; Kefford, R. F.; von Deimling, A.; Scolyer, R. A.; Long, G. V. BRAF(V600E) protein expression and outcome from BRAF inhibitor treatment in BRAF(V600E) metastatic melanoma 2013 British Journal of Cancer 108 4 924-31

189. Wu, B. J.; Li, W. P.; Qian, C.; Ding, W.; Zhou, Z. W.; Jiang, H. Serum soluble MICB (sMICB) correlates with disease progression and survival in melanoma patients 2013 Tumor Biology 34 1 565-569

190. Yaghmour, G.; Pandey, M.; Ireland, C.; Patel, K.; Nunnery, S.; Powell, D.; Baum, S.; Wiedower, E.; Schwartzberg, L. S.; Martin, M. G. Role of genomic instability in immunotherapy with checkpoint inhibitors 2016 Anticancer Research 36 8 4033-4038

191. Zimmer, L.; Eigentler, T. K.; Kiecker, F.; Simon, J.; Utikal, J.; Mohr, P.; Berking, C.; Kampgen, E.; Dippel, E.; Stadler, R.; Hauschild, A.; Fluck, M.; Terheyden, P.; Rompel, R.; Loquai, C.; Assi, Z.; Garbe, C.; Schadendorf, D. Open-label, multicenter, single-arm phase II DeCOG-study of ipilimumab in pretreated patients with different subtypes of metastatic melanoma 2015 Journal of Translational Medicine 13 (1) (no pagination) 351

192. Sileni, V. C.; Pigozzo, J.; Ascierto, P. A.; Grimaldi, A. M.; Maio, M.; Di Guardo, L.; Marchetti, P.; De Rosa, F.; Nuzzo, C.; Testori, A.; Cocorocchio, E.; Bernengo, M. G.; Guida, M.; Marconcini, R.; Merelli, B.; Parmiani, G.; Rinaldi, G.; Aglietta, M.; Grosso, M.; Queirolo, P. Efficacy and safety of ipilimumab in elderly patients with pretreated advanced melanoma treated at Italian centres through the expanded access programme 2014 Journal of Experimental and Clinical Cancer Research 33 (1) (no pagination) 30

193. Simeone, E.; Gentilcore, G.; Giannarelli, D.; Grimaldi, A. M.; Caraco, C.; Curvietto, M.; Esposito, A.; Paone, M.; Palla, M.; Cavalcanti, E.; Sandomenico, F.; Petrillo, A.; Botti, G.; Fulciniti, F.; Palmieri, G.; Queirolo, P.; Marchetti, P.; Ferraresi, V.; Rinaldi, G.; Pistillo, M. P.; Ciliberto, G.; Mozzillo, N.; Ascierto, P. A. Immunological and biological changes during ipilimumab treatment and their potential correlation with clinical response and survival in patients with advanced melanoma.[Erratum appears in Cancer Immunol Immunother. 2014 Nov;63(11):1233] 2014 Cancer Immunology, Immunotherapy 63 7 675-83

194. Ouellet, D.; Kassir, N.; Chiu, J.; Mouksassi, M. S.; Leonowens, C.; Cox, D.; DeMarini, D. J.; Gardner, O.; Crist, W.; Patel, K. Population pharmacokinetics and exposure-response of trametinib, a MEK inhibitor, in patients with BRAF V600 mutation-positive melanoma 2016 Cancer Chemotherapy and Pharmacology 77 4 807-817

A.8 Quality assessment of COLUMBUS, COMBI-v and COMBI-d

Critical appraisal of the included RCTs was conducted using the quality assessment criteria for the National Institute for health and care excellence evidence submissions [3] and the Cochrane Risk of Bias tool [4]. A summary of the quality assessment is provided in Table A. 8.

Among the seven included studies, the overall risk of bias was low in terms of the randomisation method, baseline characteristics, withdrawals or discontinuations, and statistical analyses. Higher risk of bias was observed in terms of allocation concealment and blinding for the included open-label study (i.e. COLUMBUS [27]). Details regarding the concealment of treatment allocation were usually not adequately reported. Please note that as per Cochrane Risk of Bias tool [4], allocation concealment refers to "inadequate concealment of allocations prior to assignment" or "in advance, or during, enrolment". Adequate details were only provided in the COMBI-d study [10]. The investigators, participants, and outcome assessors were appropriately blinded to treatment allocation in the one double-blind study, COMBI-d [10].

Overall, none of the studies were identified as being at a high risk of bias; hence, the validity of the results is not a primary concern for any of the included studies.

Table A. 8: Critical appraisal of the included RCTs

Criteria		COLUMBUS	COMBI-v	COMBI-d
Randomisation	Was Randomisation carried out appropriately? (yes/no/not clear/N/A)	Yes	Yes	Yes
Allocation concealment	Was the concealment of treatment allocation adequate? (yes/no/not clear/N/A)	Yes	Not clear	Yes
Baseline comparability	Were the groups similar at the outset of the study in terms of prognostic factors? (yes/no/not clear/N/A)	Yes	Yes	Yes

Criteria		COLUMBUS	COMBI-v	COMBI-d
Blinding	Were the care providers, participants and outcome assessors blind to treatment allocation? (yes/no/not clear/N/A)	NA	No	Yes, double blind
Attrition	Were there any unexpected imbalances in drop-outs between groups? (yes/no/not clear/N/A)	Not clear	No	No
Selective reporting	Is there any evidence to suggest that the authors measured more outcomes than they reported? (yes/no/not clear/N/A)	No	No	No
Analysis	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? (yes/no/not clear/N/A)	Yes	Yes	Yes

Abbreviations: *N/A: not applicable. Checklist sourced from the UK NICE technology appraisal guidance*[3]

Appendix B. HRQoL literature search

B.1 Scope of the review

The scope of the current SLR was defined in terms of criteria such as the patient population, the intervention, the comparators, the outcomes measures and the study design (PICOS Statement). Once all criteria had been specified, they were translated into "search strings" after which the search was executed, resulting in the identification of relevant and important evidence. The PICOS statement applied to this QoL part is presented in Table B. 1 below. The list of interventions was derived from the ESMO guidelines for treatment of unresectable or metastatic cutaneous melanoma [2].

Table B. 1: PICOS statement

Criteria	Definition
Patient population	Adult (18 years and older) patients with unresectable or metastatic cutaneous melanoma
Intervention	Encorafenib (combined with) binimetinib, dabrafenib, vemurafenib, trametinib, cobimetinib, ipilimumab, nivolumab, pembrolizumab (lambrolizumab), atezolizumab, talimogene, dacarbazine, temozolomide, fotemustine, vindesine, interferon, interleukin-2, taxanes, platinum derivatives (monotherapy or combination therapy (2 drugs or more))
Comparators	Any treatment from the above mentioned list of interventions (monotherapy or combination therapy (2 drugs or more)) **OR** Placebo or best supportive care
Outcomes measures	• QoL (Disease or non-disease specific e.g. FACT-M, SF36, etc.), HRQoL, functional status, well-being scores AND/OR • Utility values elicited using the following techniques: TTO, SG, Generic preference based instruments (e.g. EQ-5D, SF-36) AND/OR • Utilities derived from disease specific measures (e.g. FACT-M, EORTC QLQ-C30)
Study design	• Not restricted by design • All studies must include at least 10 melanoma patients

Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life questionnaire – Core 30; EQ-5D: EuroQol Five Dimensions questionnaire; FACT-M: Functional Assessment of Cancer Therapy-Melanoma; HRQoL: health-related quality of life; QoL: quality of life; SF-36: Short-Form 36 items health survey; SG: Standard Gamble; TTO: time trade-off

B.2 Databases used in search

The databases used in the searches are outlined below.

- MEDLINE
- Embase
- Epub ahead of print
- MEDLINE In-Process
- The Cochrane Library
    - Central register of controlled trials
    - Database of abstracts of reviews of effects

The searches were conducted using the OVID platform. The OVID platform is an accepted tool in SLRs and provides a standardised access to a wide range of clinical literature databases. Advanced searching techniques were used to increase the efficiency of the search and encompass a series of abbreviated terms (Table B. 2).

Table B. 2: Key search commands for OVID-based searches

Search Commands	Explanation
ab.	Abstract
dr	Drug Resistance
dt	Drug Therapy
Exp	Indicates that the Medical Subject Heading (MeSH) was exploded to include the narrower, more specific terms beneath it in the MeSH tree
mp.	Indicates a multi-purpose search (several fields at the time on advanced searches), looking in general into the Title, Original Title, Abstract, Subject Heading, Name of Substance, and Registry Word fields
pt.	Indicates the form of the literature (e.g. Article, book, etc...)
th	Therapy
ti.	Title
tw.	Performs a search in all the fields that contain text words and which are appropriate for a subject search (title and abstract in Medline; title abstract and drug trade name in Embase)
/	Indicates a MeSH subject with all subheadings selected
$	Indicates that the search term was truncated
?	Replaces zero or one character

B.3 Search strategies

Search strategies with the OVID platform were based on specific combinations of thematic groups. Thematic groups encompass all the possible individual search words ("search strings") that refer to or were related with an overarching topic.

The timeframe of the search was set from 2007 to present and the language of publication was restricted to English. The SLR search was conducted on 02 May 2017 and updated on 03 April 2018.

A schematic overview of the QoL search strategy is given in Table B. 3 and the detailed search strategy is provided in Table B. 4 and Table B. 5.

Table B. 3: Outline QoL search strategy

QoL Search Strategy
Thematic groups • Disease terms • QoL impact terms • Excluded terms
Combinations of thematic groups • Disease terms AND QOL impact • 1 NOT excluded terms • Limit 2 for year (2007-current) and language (English)

Abbreviations: QoL, quality of life

From the identified studies, upon removal of duplicates, references were exported to a distinct Excel spreadsheet. The relevance of every publication was assessed based on the defined eligibility criteria, commonly known as "inclusion/exclusion" criteria.

Table B. 4: QoL search strings – on 02 May 2017

#	Search term	Hits
Disease terms – unresectable or metastatic melanoma		
1	exp Melanoma/	191,375
2	melanom$.mp.	247,934
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumo?r$)).ti,ab.	69,292
4	**or/1-3**	**297,332**
5	(metasta$ or stage IIIb or stage IIIc or stage IV or unresectable$ or advanced$ or brain metasta$).mp.	1,777,861
6	exp metastasis/dr, dt, th [Drug Resistance, Drug Therapy, Therapy]	49,647
7	**5 or 6**	**1,778,327**
8	**4 and 7**	**100,446**
QoL impact terms		
9	exp "quality of life"/	529,047
10	quality of life.mp.	727,674
11	(qol or hql or hqol or hrqol).mp.	115,141
12	health related quality of life.mp.	85,690
13	quality adjusted life year/	31,646
14	(qaly$ or qualy$ or quality adjusted life or life quality or quality adjusted survival).mp.	62,694
15	exp disability/	131,926
16	q twist.mp.	340
17	(health utili$ index or hui or hui2 or hui 2 or hui3 or hui 3).mp.	4,224
18	(utili$ approach$ or health gain).mp.	1,878
19	((utili$ or preference$) and (value$ or weight$ or scor$ or index$ or measure$ or outcome$ or state$ or health or analy$)).mp.	1,256,559
20	willingness to pay.mp.	10,797
21	WTP.mp.	3,264
22	(quality of well being or qwb).mp.	1,119
23	assessment of quality of life.mp.	4,345
24	(person trade off$ or person tradeoff$ or standard gamble$ or sg or time trade off or time tradeoff or tto).mp.	22,639
25	(disutili$ or daly or disabili$ adjusted life).mp.	7,041
26	(health$ year$ equivalen$ or hye$ or health utilit$).mp.	6,626
27	rosser index.mp.	52
28	Short Form 36/	18,672
29	(short form 6d or shortform 6d or sf6d or sf 6d).mp.	2,041
30	(eq5d or eq 5d or euroqol 5d or euroqol).mp.	22,937
31	(categor$ scal$ or linear scal$ or linear analog$ scal$ or visual scal$ or visual analog scal$ or VAS or magnitude estimat$).mp.	168,793
32	visual analog scale/	59,397
33	health status indicator/	25,342
34	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	2,253
35	((mapping or regression or "cross walking" or "crosswalking") adj3 utility).mp.	597
36	(eortc qlq-c30 or fact-m).mp.	7,109
37	**Or/9-36**	**2,228,421**
38	**8 (Disease) and 37 (QoL impact)**	**4,673**

#	Search term	Hits
Exclusion terms		
39	Letter.pt.	1,644,982
40	Letter.mp.	1,703,071
41	editorial.pt.	875,346
42	comment$.pt. or comment$.mp.	931,116
43	(editorial or note).mp.	1,559,283
44	Exp Animal/ not Human/	7,337,856
45	**or/39-44**	**10,829,554**
46	**38 not 45**	**4,325**
Total clinical search		
47	**limit 46 to (english language and yr="2007-Current")**	**3,275**

Table B. 5: QoL search strings – updated on 03 April 2018

#	Search term	Hits
Disease terms – unresectable or metastatic melanoma		
1	exp Melanoma/	196,570
2	melanom$.mp.	262,040
3	(skin adj3 (cancer$ or oncolog$ or malignan$ or carcinoma$ or adenocarcinoma$ or tumo?r$)).ti,ab.	73,036
4	**or/1-3**	**313,595**
5	(metasta$ or stage IIIb or stage IIIc or stage IV or unresectable$ or advanced$ or brain metasta$).mp.	1,901,029
6	exp metastasis/dr, dt, th [Drug Resistance, Drug Therapy, Therapy]	52,763
7	**5 or 6**	**1,902,060**
8	**4 and 7**	**107,565**
QoL impact terms		
9	exp "quality of life"/	578,145
10	quality of life.mp.	802,011
11	(qol or hql or hqol or hrqol).mp.	129,585
12	health related quality of life.mp.	95,927
13	quality adjusted life year/	34,874
14	(qaly$ or qualy$ or quality adjusted life or life quality or quality adjusted survival).mp.	69,407
15	exp disability/	147,726
16	q twist.mp.	361
17	(health utili$ index or hui or hui2 or hui 2 or hui3 or hui 3).mp.	4,622
18	(utili$ approach$ or health gain).mp.	2,089
19	((utili$ or preference$) and (value$ or weight$ or scor$ or index$ or measure$ or outcome$ or state$ or health or analy$)).mp.	1,373,933
20	willingness to pay.mp.	12,268
21	WTP.mp.	3,723
22	(quality of well being or qwb).mp.	1,231
23	assessment of quality of life.mp.	4,741
24	(person trade off$ or person tradeoff$ or standard gamble$ or sg or time trade off or time tradeoff or tto).mp.	24,900
25	(disutili$ or daly or disabili$ adjusted life).mp.	8,171
26	(health$ year$ equivalen$ or hye$ or health utilit$).mp.	7,174

#	Search term	Hits
27	rosser index.mp.	53
28	Short Form 36/	21,790
29	(short form 6d or shortform 6d or sf6d or sf 6d).mp.	2,179
30	(eq5d or eq 5d or euroqol 5d or euroqol).mp.	27,044
31	(categor$ scal$ or linear scal$ or linear analog$ scal$ or visual scal$ or visual analog scal$ or VAS or magnitude estimat$).mp.	187,892
32	visual analog scale/	68,378
33	health status indicator/	25,582
34	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	2,454
35	((mapping or regression or "cross walking" or "crosswalking") adj3 utility).mp.	654
36	(eortc qlq-c30 or fact-m).mp.	8,132
37	**Or/9-36**	**2,442,614**
38	**8 (Disease) and 37 (QoL impact)**	**5,352**
Exclusion terms		
39	Letter.pt.	1,703,109
40	Letter.mp.	1,760,859
41	editorial.pt.	925,209
42	comment$.pt. or comment$.mp.	973,526
43	(editorial or note).mp.	1,659,189
44	Exp Animal/ not Human/	7,591,043
45	**or/39-44**	**11,268,762**
46	**38 not 45**	**4,882**
Total clinical search		
47	**limit 46 to (english language and yr="2007-Current")**	**3,841**

B.4 Article eligibility and study selection

Publications identified through the systematic review were evaluated in a stepwise process in order to assess whether or not they should be included for data extraction. Furthermore, an additional step was foreseen in the case uncertainty about inclusion/exclusion of the article existed. The inclusion/exclusion criteria used against the publications is in the PICOS format as in Table B. 6. This procedure complies with stringent Health technology assessment (HTA) guidelines surrounding methodology of systematic reviews and is described in steps 1 to 4, below.

Step 1: Title and abstract review

All publications were independently double reviewed based on their titles first and then abstracts against the inclusion/exclusion criteria. All papers included at the end of this stage were retained for Step 3. Papers excluded at this review stage were reported in a table format with a clear justification for their exclusion and a note of the number of papers excluded was kept for use in the PRISMA flow diagram. All publications included in the review were presented in an excel document with the title, year of publication, authors and abstract provided for review.

Articles for which uncertainty remains whether to include or exclude passed through a second step for reconciliation or arbitrage.

Step 2: Abstracts with uncertain inclusion/exclusion

Publications for which uncertainty exists on the most appropriate action (inclusion or exclusion) after being double reviewed, any disagreement was resolved either through "reconciliation" (discussion between the two reviewers) or through "arbitration" (by a third independent reviewer). In the last case, the "majority view" determined inclusion or exclusion. Retained publications passed to Step 3 (together with those retained in Step 1), whereas excluded publications were maintained in a separate sheet with a clear justification for their exclusion.

Step 3 – Full text review

Publications included after abstract review or step 2 were ordered for a full review of the text by two independent reviewers. All papers included after the full text review were retained for data extraction. A record was kept of papers excluded at this stage along with a clear justification for their exclusion.

Step 4 – Full text with uncertain inclusion/exclusion

The same procedure as described in Step 2 was considered for the full texts.

Table B. 6: Eligibility criteria for the QoL search

QoL search	Inclusion	Exclusion
Patient population	Adult (18 years and older) patients with unresectable or metastatic cutaneous melanoma	Non-human populations Patients below 18 years Patients with other types of skin cancers (non-melanoma skin cancers), such as basal cell and squamous-cell cancers, Kaposi sarcoma, and lymphoma of the skin
Intervention (monotherapy or combination therapy (2 drugs or more))	Encorafenib (combined with) binimetinib, dabrafenib, vemurafenib, trametinib, cobimetinib, ipilimumab, nivolumab, pembrolizumab (lambrolizumab), atezolizumab, talimogene, dacarbazine, temozolomide, fotemustine, vindesine, interferon, interleukin-2, taxanes, platinum derivatives (monotherapy or combination therapy (2 drugs or more))	No specific restrictions applied on interventions given the need to retrieve broad-scope patient-reported findings e.g. humanistic burden or methodological papers
Comparators[1]	Any treatment from the above mentioned list of interventions (monotherapy or combination therapy (2 drugs or more)) *OR* Placebo or best supportive care	No specific restrictions applied on comparators, see rationale above
Outcome measures	• QoL (disease or non-disease specific e.g. FACT-M, SF36, etc.), HRQoL, functional status, well-being scores *AND/OR* • Utility values elicited using the following techniques: TTO, SG, Generic preference based instruments (e.g. EQ-5D, SF-36) AND/OR • Utilities derived from disease specific measures (e.g. FACT-M, EORTC QLQ-C30)	Any not listed in the inclusion criteria

QoL search	Inclusion	Exclusion
Study design	• Not restricted by design • All studies must include at least 10 melanoma patients	Use of non-validated questionnaires. No other specific restrictions applied on design

[1] Included studies were not restricted to drug-specific studies only, but the interventions were reported among the inclusion criteria to ensure QoL of relevant drugs are extracted

Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life questionnaire – Core 30; EQ-5D: EuroQol Five Dimensions questionnaire; FACT-M: Functional Assessment of Cancer Therapy-Melanoma; HRQoL: health-related quality of life; QoL: quality of life; SF-36: Short-Form 36 items health survey; SG: Standard Gamble; TTO: time trade-off

B.5 Quality assessment strategy

The methodological quality of the studies included from the systematic review was assessed using the criteria for methodological quality indicated in the National Institute of Health and Care Excellence (NICE) Decision support unit (DSU) technical support document [28]. The quality assessment checklist of individual health state utility value studies was used to assess the relevance of the evidence as well as the quality.

B.6 Results

A summary of results for the search conducted on 02 May 2017 and 03 April 2018 are outlined in section 4.2.2 of the main document.

B.6.1 List of included studies

A list of priority 1 studies (BRAFi RCTs) is provided below. Although the scope for priority 1 studies was broader than the PICO defined by the Medicine Council, incorporating all BRAFi monotherapies and combination therapies, all studies pertaining to the intervention (Enco+Bini 450) and the comparator (Dabra+Tram) were captured in the COLUMBUS, COMBI-v and COMBI-d trials.

COLUMBUS

1. Gogas et al, 2018 [29]

   - Gogas H, Dummer R, Ascierto PA, Mandala M, Liszkay G, Garbe C, et al. Quality-of-Life (QoL) in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant Melanoma. Annals of Oncology. 2017;28 (Suppl_5):v428-v48.

COMBI-v

2. Grob et al. 2015 [30]

   - Grob JJ, Amonkar MM, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncology. 2015;16:1389-98.

3. Grob et al, 2015 (poster) [31]

    - Grob JJ, Amonkar M, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. Health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with BRAF V600 metastatic melanoma. Eur J Cancer. 2015;Volume 51, (Supplement 3):S682–S3.

COMBI-d

4. Schadendorf et al. 2015 [32]

    - Schadendorf D, Amonkar MM, Stroyakovskiy D, Levchenko E, Gogas H, de Braud F, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. European Journal of Cancer. 2015;51:833-40.

COMBi-v/COMBI-d pooled

5. Robert et al. 2016 (poster) [33]

    - Robert C, Schadendorf D, Long GV, Stroyakovskiy D, Levchenko E, Chiarion-Sileni V, et al. Analysis of patient-reported outcomes by disease progression status in patients (pts) with BRAF V600-mutant metastatic melanoma in the COMBI-d and COMBI-v trials. Annals of Oncology Conference: 41st European Society for Medical Oncology Congress, ESMO. 2016;27.

6. Grob et al. 2016 (poster) [34]

    - Grob JJ, Robert C, Long GV, Stroyakovskiy D, Levchenko E, Chiarion-Sileni V, et al. Health-related quality-of-life (HRQOL) impact of dabrafenib (D) and trametinib (T) vs *BRAF inhibitor (BRAFi) monotherapy by lactate dehydrogenase (LDH) in patients (pts) with BRAF V600-mutant melanoma. Annals of Oncology Conference: 41st European Society for Medical Oncology Congress, ESMO. 2016;27.*

CoBRIM

7. Dreno et al., 2015 (poster) [35]

    - Dreno B, Bartley K, Ascierto PA, Atkinson V, Liszkay G, Maio M, et al. Quality-of-life (QOL) assessment in patients (pts) with metastatic melanoma receiving vemurafenib (V) and cobimetinib (C). Journal of Clinical Oncology Conference. 2015;33.

8. Ascierto et al., 2016 [17]

    - Ascierto PA, McArthur GA, Dreno B, Atkinson V, Liszkay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016;17(9):1248-60.

9. Dreno et al., 2017 (poster) [36]

- Dreno B, Larkin J, McArthur G, Maio M, Demidov L, Park E, et al. Characterization of responders to cobimetinib (C) and vemurafenib (V) in patients (Pts) with BRAF-mutated metastatic melanoma (MM) in the coBRIM study. Pigment Cell and Melanoma Research. 2017;30 (1):93-4.

10. Dreno et al., 2018 [37]

- Dréno B, Ascierto PA, Atkinson V, Liszkay G, Maio M, Mandalà M, et al. Health-related quality of life impact of cobimetinib in combination with vemurafenib in patients with advanced or metastatic BRAFV600 mutation-positive melanoma. British Journal of Cancer. 2018;118:777-84.

BREAK-3

11. Grob et al. 2013 (poster) [38]

- Grob J, Algarra SM, Amonkar MM, Demidov LV, Goodman VL, Grotzinger K, et al. Dabrafenib vs dacarbazine (DTIC) in patients with BRAF V600+ advanced and metastatic melanoma in BREAK-3: Quality of life (QOL) analysis. Pigment Cell and Melanoma Research. 2013;26 (1):152.

12. Grob et al. 2014 [39]

- Grob JJ, Amonkar MM, Martin-Algarra S, Demidov LV, Goodman V, Grotzinger K, et al. Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: quality-of-life analyses of the BREAK-3 study comparing dabrafenib with dacarbazine. Annals of Oncology. 2014;25:1428-36.

B.6.2 List of excluded studies

The list of excluded studies, following full text review, including reasons for exclusion are provided in separate document entitled: PF_EncoBini_SLR_QoL_Clinical_Excluded_studies.xlsx

A list of the 91 citations excluded at full text review is also provided below:

1. Amann, V. C.; Hoffmann, D.; Mangana, J.; Dummer, R.; Goldinger, S. M. Successful Retreatment with Combined BRAF/MEK-inhibition in Metastatic BRAFV600-mutated Melanoma 2017 Journal of the European Academy of Dermatology & Venereology 12 12

2. Anforth, R.; Fernandez-Penas, P.; Long, G. V. Cutaneous toxicities of RAF inhibitors 2013 Lancet Oncology 14 1 e11-8

3. Bagge, A. L.; Ben-Shabat, I.; Belgrano, V.; Olofsson Bagge, R. Erratum to: Health-Related Quality of Life for Patients Who have In-Transit Melanoma Metastases Treated with Isolated Limb Perfusion.[Erratum for Ann Surg Oncol. 2016 Jun;23(6):2062-9; PMID: 26868956] 2016 Annals of Surgical Oncology 23 Suppl 5 1057

4. Bastiaannet, E.; Hoekstra-Weebers, J. E.; Francken, A. B.; Jager, P. L.; Van Der Jagt, E. J.; Hoekstra, H. J. Perception of burden experienced during diagnostic tests by melanoma patients with lymph node metastases 2009 Melanoma Research 19 1 36-41

5. Brandberg, Y.; Johansson, H.; Aamdal, S.; Bastholt, L.; Hernberg, M.; Stierner, U.; von der Maase, H.; Hansson, J.; Nordic Melanoma Cooperative, Group Role functioning before start of adjuvant

treatment was an independent prognostic factor for survival and time to failure. A report from the Nordic adjuvant interferon trial for patients with high-risk melanoma 2013 Acta Oncologica 52 6 1086-93

6. Campolmi, E.; Mugnai, F.; Riccio, M.; Grifoni, R.; Gunnella, S.; Fortunato, S.; Fioretto, L.; Borgognoni, L.; Pimpinelli, N. Body image and awareness in patients with advanced-stage melanoma 2016 Giornale Italiano di Dermatologia e Venereologia 151 4 327-31

7. Chin-Lenn, L.; Temple-Oberle, C.; McKinnon, J. G. Isolated limb infusion: Efficacy, toxicity and an evolution in the management of in-transit melanoma 2015 Plastic Surgery 23 1 25-30

8. Coens, C.; Suciu, S.; Chiarion-Sileni, V.; Grob, J. J.; Dummer, R.; Wolchok, J. D.; Schmidt, H.; Hamid, O.; Robert, C.; Ascierto, P. A.; Richards, J. M.; Lebbe, C.; Ferraresi, V.; Smylie, M.; Weber, J. S.; Maio, M.; Bottomley, A.; Kotapati, S.; de Pril, V.; Testori, A.; Eggermont, A. M. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial 2017 Lancet Oncology 18 3 393-403

9. Corrie, P. G.; Marshall, A.; Dunn, J. A.; Middleton, M. R.; Nathan, P. D.; Gore, M.; Davidson, N.; Nicholson, S.; Kelly, C. G.; Marples, M.; Danson, S. J.; Marshall, E.; Houston, S. J.; Board, R. E.; Waterston, A. M.; Nobes, J. P.; Harries, M.; Kumar, S.; Young, G.; Lorigan, P. Adjuvant bevacizumab in patients with melanoma at high risk of recurrence (AVAST-M): preplanned interim results from a multicentre, open-label, randomised controlled phase 3 study.[Erratum appears in Lancet Oncol. 2014 Aug;15(9):e365], [Erratum appears in Lancet Oncol. 2014 Jun;15(7):e253] 2014 Lancet Oncology 15 6 620-30

10. Dhillon, S. Dabrafenib plus Trametinib: a Review in Advanced Melanoma with a BRAF (V600) Mutation 2016 Targeted Oncology 11 3 417-28

11. Eggermont, A. M. Adjuvant ipilimumab in stage III melanoma: New landscape, new questions 2016 European Journal of Cancer 69 39-42

12. Eigentler, T. K.; Gutzmer, R.; Hauschild, A.; Heinzerling, L.; Schadendorf, D.; Nashan, D.; Holzle, E.; Kiecker, F.; Becker, J.; Sunderkotter, C.; Moll, I.; Richtig, E.; Ponitzsch, I.; Pehamberger, H.; Kaufmann, R.; Pfohler, C.; Vogt, T.; Berking, C.; Praxmarer, M.; Garbe, C.; Dermatologic Cooperative Oncology, Group Adjuvant treatment with pegylated interferon alpha-2a versus low-dose interferon alpha-2a in patients with high-risk melanoma: a randomized phase III DeCOG trial 2016 Annals of Oncology 27 8 1625-32

13. Harrison, J. P.; Kim, H. Progressive Disease Does Not Impact Hrqol In Patients Receiving Nivolumab For The Treatment Of Unresectable Or Metastatic Melanoma 2015 Value in Health 18 7 A475

14. Hauswald, H.; Habl, G.; Krug, D.; Kehle, D.; Combs, S. E.; Bermejo, J. L.; Debus, J.; Sterzing, F. Whole brain helical Tomotherapy with integrated boost for brain metastases in patients with malignant melanoma-a randomized trial 2013 Radiation Oncology 8 234

15. Jochems, A.; Schouwenburg, M. G.; Leeneman, B.; Franken, M. G.; van den Eertwegh, A. J.; Haanen, J. B.; Gelderblom, H.; Uyl-de Groot, C. A.; Aarts, M. J.; van den Berkmortel, F. W.; Blokx, W. A.; Cardous-Ubbink, M. C.; Groenewegen, G.; de Groot, J. W.; Hospers, G. A.; Kapiteijn, E.; Koornstra, R. H.; Kruit, W. H.; Louwman, M. W.; Piersma, D.; van Rijn, R. S.; Ten Tije, A. J.; Vreugdenhil, G.; Wouters, M. W.; van der Hoeven, J. J. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands 2017 European Journal of Cancer 72 156-165

16. Li, R. H.; Hou, X. Y.; Yang, C. S.; Liu, W. L.; Tang, J. Q.; Liu, Y. Q.; Jiang, G. Temozolomide for Treating Malignant Melanoma 2015 Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan 25 9 680-8

17. Mohr, P.; Hauschild, A.; Enk, A.; Trefzer, U.; Rass, K.; Grabbe, S.; Brockmeyer, N. H.; Koller, J.; Gogas, H.; Weichenthal, M. Intermittent high-dose intravenous interferon alpha 2b (IFNa2b) for adjuvant treatment of stage III malignant melanoma: An interim analysis of a randomized phase III study (NCT00226408) 2008 Journal of Clinical Oncology 26 15_suppl 9040

18. Mohr, P.; Hauschild, A.; Trefzer, U.; Enk, A.; Tilgen, W.; Loquai, C.; Gogas, H.; Haalck, T.; Koller, J.; Schadendorf, D.; Dummer, R.; Gutzmer, R.; Brockmeyer, N.; Holzle, E.; Sunderkotter, C.; Mauch, C.; Stein, A.; Schneider, L.; Podda, M.; Weichenthal, M. Intermittent high-dose intravenous interferon alpha 2b (IFNa2b) for adjuvant treatment of stage III malignant melanoma: Final analysis of a randomized phase III DeCOG-trial (NCT00226408) 2012 Journal of Clinical Oncology. Conference 30 15 SUPPL. 1

19. Nicolussi, A. C.; Sawada, N. O.; Andrade, V.; Paula, J. M.; Meneghini, A. C. Health-related quality of life of cancer patients undergoing chemotherapy 2012 Supportive Care in Cancer 20 S80-S81

20. Noorda, E. M.; van Kreij, R. H.; Vrouenraets, B. C.; Nieweg, O. E.; Muller, M.; Kroon, B. B.; Aaronson, N. K. The health-related quality of life of long-term survivors of melanoma treated with isolated limb perfusion 2007 European Journal of Surgical Oncology 33 6 776-82

21. Perez Segura, P.; Gil, M.; Balana, C.; Chacon, I.; Munoz Langa, J.; Martin, M. Phase II trial of temozolomide for leptomeningeal metastases: Safety and activity analysis 2010 Journal of Clinical Oncology. Conference 28 15 SUPPL. 1

22. Petrella, T.; Quirt, I.; Verma, S.; Haynes, A. E.; Charette, M.; Bak, K. Single-agent interleukin-2 in the treatment of metastatic melanoma 2007 Current Oncology 14 1 21-26

23. Porter, J.; Lee, D.; Hertel, N.; Hatswell, A. J. Patient Reported Utilities In First-Line Advanced Or Metastatic Melanoma: Analysis Of Trial CA184-024 2014 Value in Health 17 7 A569

24. Quirbt, I.; Verma, S.; Petrella, T.; Bak, K.; Charette, M.; Members of the Melanoma Disease Site Group of Cancer Care Ontario's Program in Evidence-Based, Care Temozolomide for the treatment of metastatic melanoma 2007 Current Oncology 14 1 27-33

25. Quirt, I.; Verma, S.; Petrella, T.; Bak, K.; Charette, M. Temozolomide for the treatment of metastatic melanoma: A systematic review 2007 Oncologist 12 9 1114-1123

26. Schwartzentruber, D. J.; Lawson, D.; Richards, J.; Conry, R. M.; Miller, D.; Triesman, J.; Gailani, F.; Riley, L. B.; Vena, D.; Hwu, P. A phase III multi-institutional randomized study of immunization with the gp100: 209-217(210M) peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma 2009 Journal of Clinical Oncology 1) CRA9011

27. Shafrin, J.; Schwartz, T. T.; Okoro, T.; Romley, J. A. Patient Versus Physician Valuation of Durable Survival Gains: Implications for Value Framework Assessments 2017 Value in Health 20 2 217-223

28. Testori, A. Electrochemotherapy with bleomycin: A local treatment with possible systemic implication 2010 Pigment Cell and Melanoma Research 23 (6) 882

29. Trotter, J.; Middleton, M.; Kotapati, S.; Brokaw, J.; Gates, C.; Abernethy, A. IMAGE: A 'real world' multinational observational study in patients with advanced melanoma 2012 Pigment Cell and Melanoma Research 25 (6) 893

30. Yeung, C.; Petrella, T. M.; Wright, F. C.; Abadir, W.; Look Hong, N. J. Topical immunotherapy with diphencyprone (DPCP) for in-transit and unresectable cutaneous melanoma lesions: an inaugural Canadian series 2017 Expert Review of Clinical Immunology 13 4 383-388

31. Anonymous, Society for Melanoma Research 2012 Congress 2012 Pigment Cell and Melanoma Research. Conference: Society for Melanoma Research 26 1

32. Anonymous, Abstracts from the 16th World Congress on Cancers of the Skin 2016 2016 Melanoma Research. Conference: 16th World Congress on Cancers of the Skin 26 no pagination

33. Bagge, A. S. L.; Ben-Shabat, I.; Belgrano, V.; Olofsson Bagge, R. Health-Related Quality of Life for Patients Who have In-Transit Melanoma Metastases Treated with Isolated Limb Perfusion 2016 Annals of Surgical Oncology 23 6 2062-2069

34. Bagge, A. S. L.; Ben-Shabat, I.; Belgrano, V.; Olofsson Bagge, R. Erratum to: Health-Related Quality of Life for Patients Who have In-Transit Melanoma Metastases Treated with Isolated Limb Perfusion (Ann Surg Oncol, 10.1245/S10434-016-5103-9) 2016 Annals of Surgical Oncology 23 1057

35. Belum, V. R.; Fischer, A.; Choi, J. N.; Lacouture, M. E. Dermatological adverse events from BRAF inhibitors: A growing problem 2013 Current Oncology Reports 15 3 249-259

36. Buss, M. K.; De Santo-Madeya, S.; Lynch, J.; Zerillo, J. A.; McDermott, D. F. Integrating palliative care into care of patients with kidney cancer and melanoma 2014 Journal of Clinical Oncology. Conference: Palliative Care in Oncology Symposium 32 31 SUPPL. 1

37. Chen, E.; Cella, D.; Zeng, L.; Thavarajah, N.; Zhang, L.; Chang, E.; Sahgal, A.; Bennett, M.; Peckham, K.; De Costa, S.; Beaumont, J.; Tsao, M.; Danjoux, C.; Barnes, E.; Chow, E. Content validation of the FACT-Br with patients and health-care professionals to assess quality of life in patients with brain metastases 2014 Journal of Radiation Oncology 3 1 105-113

38. Corrie, P.; Marshall, A.; Goonewardena, M.; Dunn, J. A.; Middleton, M. R.; Nathan, P. D.; Gore, M. E.; Davidson, N.; Nicholson, S.; Kelly, C. G.; Marples, M.; Danson, S.; Marshall, E.; Houston, S.; Board, R. E.; Waterston, A. M.; Nobes, J.; Harries, M.; Barber, J.; Lorigan, P. Adjuvant bevacizumab as treatment for melanoma patients at high risk of recurrence: Preplanned interim results for the AVAST-M trial 2013 Journal of Clinical Oncology. Conference 31 18 SUPPL. 1

39. Corrie, P. G.; Marshall, A.; Dunn, J. A.; Middleton, M. R.; Nathan, P. D.; Gore, M.; Davidson, N.; Nicholson, S.; Kelly, C. G.; Marples, M.; Danson, S. J.; Marshall, E.; Houston, S. J.; Board, R. E.; Waterston, A. M.; Nobes, J. P.; Harries, M.; Kumar, S.; Young, G.; Lorigan, P. Adjuvant bevacizumab in patients with melanoma at high risk of recurrence (AVAST-M): Preplanned interim results from a multicentre, open-label, randomised controlled phase 3 study 2014 The Lancet Oncology 15 6 620-630

40. De Paula, L. C. L.; Fonseca, F.; Perazzo, F.; Cruz, F. M.; Cubero, D.; Trufelli, D. C.; Martins, S. P. D. S.; Santi, P. X.; Da Silva, E. A.; Del Giglio, A. Uncaria tomentosa (Cat's Claw) improves quality of life in patients with advanced solid tumors 2015 Journal of Alternative and Complementary Medicine 21 1 22-30

41. Dhillon, S. Dabrafenib plus Trametinib: a Review in Advanced Melanoma with a BRAF ^{V600} Mutation 2016 Targeted Oncology 11 3 417-428

42. Di Giacomo, A. M.; Annesi, D.; Ascierto, P. A.; Calabra, L.; Chiarion-Sileni, V.; Danielli, R.; Del Vecchio, M.; Ferraresi, V.; Ferrucci, P. F.; Fonsatti, E.; Guida, M.; Giannarelli, D.; Guidoboni, M.; Mandala, M.; Quaglino, P.; Queirolo, P.; Maccalli, C.; Parmiani, G.; Maio, M. A randomized, phase III study of fotemustine versus the combination of fotemustine and ipilimumab or the combination of ipilimumab and nivolumab in patients with metastatic melanoma with brain metastasis: The NIBIT-M2 trial 2015 Journal of Clinical Oncology 33 15 SUPPL. 1 CONFERENCE START: 2015 May 29 CONFERENCE END: 2015 Jun 2

43. Di Giacomo, A. M.; Maio, M. A randomized, phase III study of fotemustine versus the combination of fotemustine and ipilimumab or the combination of ipilimumab and nivolumab in patients with melanoma with brain metastasis: The NIBIT-M2 study 2015 Annals of Oncology 26 viii5

44. Centre for Reviews and Dissemination Temozolomide for the treatment of metastatic melanoma: a systematic review (Provisional abstract) 2015 Database of Abstracts of Reviews of Effects 2

45. Drabe, N.; Jenewein, J.; Weidt, S.; Seiler, A.; Witzemann, L.; Meier, C.; Buchi, S.; Schad, K.; Nunez, D. G. When it can't been healed: A longitudinal qualitative study of relationship changes in couples facing advanced melanoma 2014 Psycho-Oncology 23 363

46. Dummer, R.; Gutzmer, R.; Corrie, P.; Millward, M.; Murzhenko, A.; Maio, M. Trial in progress: Clinical trial of nivolumab combined with ipilimumab followed by nivolumab monotherapy as first-line therapy of patients with stage III (unresectable) or stage IV melanoma: CheckMate 401 2016 Melanoma Research 26 e43

47. Eigentler, T. K.; Gutzmer, R.; Hauschild, A.; Kampgen, E.; Schadendorf, D.; Nashan, D.; Holzle, E.; Trefzer, U.; Becker, J. C.; Sunderkotter, C.; Moll, I.; Richtig, E.; Ponitzsch, I.; Pehamberger, H.; Kaufmann, R.; Pfoehler, C.; Vogt, T.; Berking, C.; Praxmarer, M.; Garbe, C. Adjuvant therapy with pegylated interferon alfa-2a (PEG-IFN) versus low-dose interferon alfa-2a (IFN) in patients with malignant melanoma in stages IIa(T3a): IIIb (AJCC 2002)-Decog-trial 2014 Journal of Clinical Oncology 32 15 SUPPL. 1 CONFERENCE START: 2014 May 30 CONFERENCE END: 2014 Jun 3

48. Fallowfield, L.; May, S.; Catt, S.; Shilling, V.; Matthews, L.; Jenkins, V. Patients' understanding about the therapeutic aims of novel drugs shown only to offer PFS benefit 2015 European Journal of Cancer 51 S216

49. Fallowfield, L.; Nadler, E.; Abernethy, A. P.; Gilloteau, I.; Greaney, M.; Gater, A.; Orsini, L.; Subar, M.; Dastani, H. B.; Lyman, G. H. Quality of survival (QoS) concept framework to assess the quality of prolonged life in advanced melanoma (MEL): Principles and application related to treatment with nivolumab (NIVO) 2015 European Journal of Cancer 51 S674-S675

50. Fallowfield, L. J.; Catt, S. L.; May, S. F.; Matthews, L.; Shilling, V. M.; Simcock, R.; Westwell, S.; Jenkins, V. A. Therapeutic aims of drugs offering only progression-free survival are misunderstood by patients, and oncologists may be overly optimistic about likely benefits 2017 Supportive Care in Cancer 25 1 237-244

51. Flaherty, K.; Arenberger, P.; Ascierto, P. A.; De Groot, J. W.; Hallmeyer, S.; Long, G. V.; Lotem, M.; Marples, M.; Schadendorf, D.; Starodub, A.; Taylor, M. H.; Wolter, P.; Yamazaki, N.; Wasserman, E.; Ford, J.; Weill, M.; Dummer, R. NEMO: A phase 3 trial of binimetinib (MEK162) versus dacarbazine in patients with untreated or progressed after first-line immunotherapy unresectable or metastatic NRAS-mutant cutaneous melanoma 2014 Journal of Clinical Oncology. Conference 32 15 SUPPL. 1

52. Franken, M.; Leeneman, B.; Schouwenburg, M.; Jochems, A.; Wouters, M.; Van Den Eertwegh, F.; Haanen, J.; Van Der Hoeven, K.; Uyl-De Groot, C. The Dutch melanoma treatment registry as blueprint for using registry data to improve health care decision making 2015 Value in Health 18 (7) A491

53. Gilbertson-White, S.; Aouizerat, B. E.; Jahan, T.; Paul, S. M.; West, C.; Schumacher, K.; Dodd, M. J.; Rabow, M.; Abu Raddaha, A. H.; Miaskowski, C. Determination of cutpoints for low and high number of symptoms in patients with advanced cancer 2012 Journal of Palliative Medicine 15 9 1027-1036

54. Godard, C.; Wang, J.; Gauthier, A.; Levy-Bachelot, L.; Annemans, L. Cost-effectiveness of pembrolizumab for treating previously untreated metastatic melanoma patients in France 2016 Value in Health Conference: ISPOR 19th annual european congress. Austria. Conference start:. 20161029. Conference end: 20161102 19 7 A730

55. Godard, C.; Wang, J.; Gauthier, A.; Levy-Bachelot, L.; Annemans, L. Cost-effectiveness of pembrolizumab for treating previously untreated metastatic melanoma patients in France 2016 Value in Health 19 (7) A730

56. Grossmann, K. F.; Othus, M.; Tarhini, A. A.; Patel, S. P.; Kirkwood, J. M.; Moon, J.; Sondak, V. K.; Ribas, A. SWOG S1404: A phase III randomized trial comparing high dose interferon to pembrolizumab in patients with high risk resected melanoma 2015 Journal of Clinical Oncology 33 15 SUPPL. 1 CONFERENCE START: 2015 May 29 CONFERENCE END: 2015 Jun 2

57. Grossmann, K. F.; Othus, M.; Tarhini, A. A.; Patel, S. P.; Moon, J.; Sondak, V. K.; Kirkwood, J. M.; Ribas, A. SWOG S1404: A phase III randomized trial comparing standard of care adjuvant therapy to pembrolizumab in patients with high risk resected melanoma 2016 Journal of Clinical Oncology. Conference 34 no pagination

58. Harrison, J. P.; Kim, H. Progressive disease does not impact HRQOL in patients receiving nivolumab for the treatment of unresectable or metastatic melanoma 2015 Value in Health 18 (7) A475

59. Hatswell, A. J.; Pennington, B.; Pericleous, L.; Rowen, D.; Lebmeier, M.; Lee, D. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death 2014 Health and Quality of Life Outcomes 12 (1) (no pagination) 140

60. Kaufman, H. L.; Silk, A.; Mehnert, J.; Gabrail, N.; Bryan, J.; Medina, D.; Bommareddy, P. K.; Shafren, D.; Grose, M.; Zloza, A. Interim results of the CAPRA clinical trial: CAVATAK and pemrolizumab in advanced melanoma 2016 Journal for ImmunoTherapy of Cancer. Conference: 31st Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer, SITC 4 no pagination

61. Kirkwood, J. M.; Ramsey, S.; Margolin, K.; Tawbi, H.; Khushalani, N.; Hallmeyer, S.; Hamid, O.; McWilliams, R.; Rao, S.; Frantz, B.; Lee, S.; Bartell, H.; McDermott, D. F. OPTIMIzE: A US multi-site observational study in patients with unresectable and metastatic melanoma (MEL) 2017 Pigment Cell and Melanoma Research 30 (1) 110

62. Kotapati, S.; Francis, S.; Sherrill, B. Health related quality of life (HRQL) of patients receiving ipilimumab with dacarbazine as first-line treatment for unresectable stage III/IV melanoma Pigment Cell & Melanoma Research 24 5 1037

63. Li, H.; Liu, L.; Zhao, X.; Huang, J.; Yang, S.; Zhang, Y. Autologous cytokine-induced killer cells combined with conventional therapy to treat malignant melanoma-a retrospective study 2015 Cytotherapy 1) S21

64. Liu, F. X.; Witt, E. A.; Ebbinghaus, S.; Beyer, G. D.; Basurto, E.; Shinde, R.; Joseph, R. Patient preferences for treatment options in advanced melanoma 2017 Pigment Cell and Melanoma Research 30 (1) 117

65. Long, G.; Dummer, R.; Flaherty, K.; Schadendorf, D.; Arenberger, P.; Demidov, L.; Di Giacomo, A. M.; Mandala, M.; Rangoni, G.; Wolter, P.; Yamazaki, N.; Ford, J.; Wasserman, E.; Weill, M.; Ascierto, P. NEMO: A phase 3 trial of binimetinib (MEK162) versus dacarbazine in patients with advanced NRAS-mutant melanoma who are untreated or have progressed on or after immunotherapy 2014 Cancer Research. Conference: AACR Special Conference on Advances in Melanoma: From Biology to Therapy 75 14 SUPPL. 1

66. Long, G. V.; Atkinson, V.; Ascierto, P. A.; Robert, C.; Hassel, J. C.; Rutkowski, P.; Savage, K. J.; Taylor, F.; Coon, C.; Gilloteau, I.; Dastani, H. B.; Waxman, I.; Abernethy, A. P. Effect of nivolumab (NIVO) on quality of life (QoL) in patients (pts) with treatment-naive advanced melanoma (MEL): Results of a phase III study (CheckMate 066) 2015 Annals of Oncology. Conference: 17th National Congress of Medical Oncology Rome Italy. Conference Start 26

67. Lynch, J. A.; DeSanto-Madeya, S.; Zerillo, J. A.; Gregas, M.; McDermott, D. F.; Mukamal, K. J.; Buss, M. K. Impact of integrated palliative care model on end-of-life (EOL) quality metrics for patients with kidney cancer (RCC) and melanoma (M) 2015 Journal of Clinical Oncology. Conference 33 29 SUPPL. 1

68. Marriott, E.; Praet, C.; Aguiar-Ibanez, R.; Pellissier, J.; Xu, R.; Wang, J. Cost-effectiveness of pembrolizumab for unresectable metastatic melanoma after progression with ipilimumab in England 2015 Value in Health 18 (7) A453

69. Pham, A.; Yondorf, M. Z.; Parashar, B.; Scheff, R. J.; Pannullo, S. C.; Ramakrishna, R.; Stieg, P. E.; Schwartz, T. H.; Wernicke, A. G. Neurocognitive function and quality of life in patients with newly diagnosed brain metastasis after treatment with intra-operative cesium-131 brachytherapy: a prospective trial 2016 Journal of Neuro-Oncology 127 1 63-71

70. Postmus, D.; Mavris, M.; Hillege, H. L.; Salmonson, T.; Ryll, B.; Plate, A.; Moulon, I.; Eichler, H. G.; Bere, N.; Pignatti, F. Incorporating patient preferences into drug development and regulatory decision making: Results from a quantitative pilot study with cancer patients, carers, and regulators 2016 Clinical Pharmacology and Therapeutics 99 5 548-554

71. Pulenzas, N.; Ray, S.; Zhang, L.; McDonald, R.; Cella, D.; Rowbottom, L.; Sahgal, A.; Soliman, H.; Tsao, M.; Danjoux, C.; Lechner, B.; Chow, E. The Brain Symptom and Impact Questionnaire in brain metastases patients: A prospective long-term follow-up study 2016 CNS Oncology 5 1 31-40

72. Robert, C.; Antonio Ascierto, P.; Maio, M.; Hernberg, M.; Schmidt, H.; Waxman, I.; Garbe, C.; Lebbe, C.; Hauschild, A. A phase III, randomized, double-blind study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus dacarbazine in patients (pts) with previously untreated, unresectable, or metastatic melanoma (MEL) 2013 Journal of Clinical Oncology. Conference 31 15 SUPPL. 1

73. Rouanne, M.; Massard, C.; Hollebecque, A.; Rousseau, V.; Varga, A.; Gazzah, A.; Neuzillet, Y.; Lebret, T.; Soria, J. C. Evaluation of sexuality, health-related quality-of-life and depression in advanced cancer patients: A prospective study in a Phase i clinical trial unit of predominantly targeted anticancer drugs 2013 European Journal of Cancer 49 2 431-438

74. Schadendorf, D.; Ascierto, P.; Dummer, R.; Long, G. V.; Arenberger, P.; Demidov, L.; Maria Di Giacomo, A.; Mandala, M.; Rangoni, G.; Wolter, P.; Yamazaki, N.; Ford, J.; Wasserman, E.; Weill, M.; Flaherty, K. T. A Phase 3 trial of binimetinib (MEK162) versus dacarbazine in patients with advanced nras-mutant melanoma who are untreated or have progressed on or after immunotherapy 2014 Pigment Cell and Melanoma Research 27 (6) 1226

75. Stenehjem, D.; Korytowsky, B.; Oderda, G.; Wanishayakorn, T.; Bauer, H.; Brixner, D. Understanding the impact of patient and physician preferences in personalized treatment for melanoma using a discrete choice experiment 2015 Value in Health 18 (7) A469-A470

76. Subbiah, V.; Bang, Y. J.; Lassen, U. N.; Wainberg, Z. A.; Soria, J. C.; Wen, P. Y.; Zenz, T.; Moreau, P.; Brunsvig, P.; De Braud, F. G.; De Greve, J.; De Jonge, M. J.; Hofheinz, R. D.; Italiano, A.; Stein, A.; Willenbacher, W.; Schellens, J. H. M.; Zielinski, C.; Rangwala, F. A.; Kreitman, R. J. ROAR: A phase 2, open-label study in patients (PTS) with BRAF V600E-mutated rare cancers to investigate the efficacy and safety of dabrafenib (D) and trametinib (T) combination therapy 2016 Journal of Clinical Oncology. Conference 34 no pagination

77. Tazi, K.; Chiuzan, C.; Shirai, K. Survival of melanoma patients with brain metastases treated with ipilimumab combined with stereotactic radiosurgery 2013 Journal of Clinical Oncology. Conference 31 15 SUPPL. 1

78. Wang, J.; Chabot, I.; El-Hadi, W.; Xu, R.; Pellissier, J.; Iliopoulos, I. Cost-effectiveness of pembrolizumab (keytruda) versus ipilimumab in patients with advanced melanoma in canada 2016 Value in Health 19 (3) A153-A154

79. Weingartner, V.; Dargatz, N.; Weber, C.; Mueller, D.; Stock, S.; Voltz, R.; Gaertner, J. Patient reported outcomes in randomized controlled cancer trials in advanced disease: a structured literature review 2016 Expert Review of Clinical Pharmacology 9 6 821-829

80. Wichtowski, M.; Murawa, D.; Czarnecki, R.; Witkiewicz, W. Electrochemotherapy as palliative treatment in patients with skin metastases 2016 European Journal of Surgical Oncology 42 (9) S132-S133

81. Yee, M. K.; Lin, Y.; Gorantla, V. C.; Butterfield, L. H.; Kluger, H. M.; Chapman, P. B.; Gangadhar, T. C.; Milhem, M. M.; Pavlick, A. C.; Amaravadi, R. K.; Schuchter, L. M.; Tarhini, A. A.; Kirkwood, J. M.; Tawbi, H. A. H. Phase 2 study of cobimetinib in combination with vemurafenib in active melanoma brain metastases (coBRIM-B) 2015 Journal of Clinical Oncology. Conference 33 15 SUPPL. 1

82. Weitman, E. S.; Perez, M.; Thompson, J. F.; Andtbacka, R. H. I.; Dalton, J.; Martin, M. L.; Miller, T.; Gwaltney, C.; Sarson, D.; Wachter, E.; Zager, J. S. Quality of life patient-reported outcomes for locally advanced cutaneous melanoma 2018 Melanoma Research 28 2 134-142

83. Weitman, E.; Perez, M. C.; Thompson, J. F.; Andtbacka, R.; Dalton, J.; Martin, M.; Miller, T.; Gwaltney, C.; Sarson, D.; Wachter, E.; Zager, J. S. Assessment of quality of life in patients with locally advanced cutaneous melanoma using patient-reported outcomes 2018 Annals of Surgical Oncology 25 (1 Supplement 1) S178

84. Mott, F. E. Patient Reported Outcomes (PROs) as Part of Value-Based Care Can Shape Therapy Guidelines: Impact on Emerging Targeted Agents and Immunotherapy Protocols in Resource-Limited Regions 2017 Oncology and Therapy 5 1 69-74

85. Huynh, E.; Rose, J.; Lambides, M.; Cong, K.; Herawati, L.; Del Cuore, M. Preferences for advanced melanoma Immuno-Oncology treatments 2018 Pigment Cell and Melanoma Research 31 (1) 149

86. Milne, D.; Billett, A.; Gough, K.; Krishnasamy, M. Managing treatmentand side effects: Exploring the experience of people undergoing immunotherapies for advanced melanoma and for those caring forthem 2017 Supportive Care in Cancer 25 (2 Supplement 1) S262-S263

87. Milne, D.; Billett, A.; Gough, K.; Krishnasamy, M. Exploring the experiences of people living with and beyond treatment for advanced melanoma and for those caring for them 2017 Psycho-Oncology 26 (Supplement 3) 24-25

88. Milne, D. Nurses role in the assessment and management of patients on I-O drugs 2017 Asia-Pacific Journal of Clinical Oncology 13 (Supplement 4) 87-88

89. Miller, T.; Zager, J. S.; Gwaltney, C.; Fippin, L.; Hansen, S.; Sarson, D.; Andtbacka, R. H.; Thompson, J. F.; Sadler, M.; Martin, M. L.; Wachter, E. Qualitative study to identify patient-perceived impacts of locally advanced cutaneous 2017 Quality of Life Research 26 (1 Supplement 1) 132-133

90. Larkin, M.; Williams, H.; Nixon, A. Digital real-world evidence platform: Taking the burden out of melanoma pain reporting 2017 Value in Health 20 (9) A453

91. Gonzalez, J. M.; Posner, J.; Lees, M. Caregiver preferences for increasing patient survival in advanced melanoma. Brett 2017 Journal of Clinical Oncology. Conference 35 5 Supplement 1

B.7 Quality assessment of COLUMBUS, COMBI-v and COMBI-d studies

The critical appraisal of the included RCTs that assessed health state utility values was conducted using the specific checklist recommended by the NICE Decision Support Unit [28]. A summary of the assessment is provided in Table B. 7.

Among the studies collecting individual EQ-5D utility scores, no major quality issues were noted in terms of the population inclusion/exclusion criteria. EQ-5D completion rates were high, at 80-95% across targeted therapy arms at the time of publication. Generally, the completion rates of HRQoL tools were high at each visit in all studies: ≥80% of available patients at each time point until Week 48 and ≥70% at disease progression in COMBI-d [32] and COMBI-v [30,31], QLQ-C30 and FACT-M completion rates >82% for all treatment arms in COLUMBUS [29].

The quality of the evidence can be limited however, by the limited data available post-progression (COLUMBUS), the exploratory nature of QoL endpoints as studies were not powered to estimate QoL endpoints, and the open label design of COMBI-v and COLUMBUS.

Table B. 7: Critical appraisal of the included RCTs - checklist specific to Health State Utility Value studies

Criteria	Question	COLUMBUS	COMBI-v	COMBI-d
Sample size	*This is not an exclusion criteria, but the precision of the estimate should be reflected in the variance around any estimate used in a model*	Standard errors are provided	Standard errors/deviations are provided	Standard errors/deviations are provided
Respondent selection and recruitment	*Does this result in a population comparable to that being modelled?*	Yes	Yes	Yes
Inclusion/ exclusion criteria	*Do these exclude any individuals? (e.g. the very elderly >80 years old are often not included in studies)*	No	No	No
Response rates to instrument used to	*Are response rates reported and if so, are the rates likely to be a threat to validity?*	Ranging from 82 – 100% for the FACT-M and 82 – 96% for the EORTC QLQ-C30	>95% at baseline, > 80% at all assessments until wk. 56, and >70% at disease progression	>90% in most cases
Loss to follow-up	*How large is the loss to follow-up and are the reasons given?* *Are these likely to threaten the validity of the estimates?*	No unbalanced drop-out rates	No unbalanced drop-out rates	No unbalanced drop-out rates
Missing data	*What are the levels of missing data and how are they dealt with?* *Again, could this threaten the validity of the estimates?*	Low level of missing answers	Low level of missing EQ-5D answers	Low level of missing EQ-5D answers
Any other problems with the study	*Example: Relevance of location (e.g. if patients recruited in non-UK country)*	Open-label design. QoL was an exploratory endpoint	Open-label design. QoL was an exploratory endpoint.	EQ-5D scores over time not published.

Abbreviations: Dabra: dabrafenib; EQ-5D: EuroQol 5-dimensions questionnaire; HSUV: health state utility value studies; QoL: quality of life; wk.: week. Sources for health states utility scores were UK NICE technology appraisals[40–42]

Appendix C. Comparative analysis: further information

C.1 Assessment of effect modification and risk of bias

When conducting evidence synthesis, it is important to assess the extent to which the included studies are subject to effect modification since this can inform the modelling approach *a priori* and help with interpretation of results post-analysis. Some examples of study level effect modifiers are: differences in patient population, differences in outcome definition, and differences in study design [43] .

To understand how effect modifiers might impact the results of evidence synthesis it helps to make a distinction between heterogeneity and inconsistency. Heterogeneity and inconsistency are caused by the same underlying mechanisms – the presence of study level effect modifiers – but manifest in different ways. In general, effect modification may occur due to imbalances of effect modifiers across studies (heterogeneity) or across comparisons (inconsistency). Heterogeneity in evidence synthesis occurs when multiple studies compare the same treatments but are subject to different levels of effect modification and has implications for generalisability of results. Inconsistency occurs due to an imbalance of effect modifiers between comparisons and leads to biased estimates of treatment effect [43].

The main effect modifiers investigated in the feasibility assessment were based mainly on patient baseline characteristics reported in the COLUMBUS and COMBI-v studies, and comprised the following:

- Age, mean/median (years)
- Gender, male/female (%)
- Previous (immuno)-therapy (%)
- ECOG performance status 0/1 (%)
- BRAF mutation V600E/K (%)
- Metastasis stage, M1c (%)
- LDH, ULN (%)
- Study design (including crossover adjustment) and inclusion criteria
- Number of metastatic sites.

These potential effect modifiers were assessed to determine heterogeneity by examining differences across studies eligible for inclusion in the indirect treatment evidence (ITC), based on available evidence.

C.1.1 Patient baseline characteristics, study design and inclusion criteria

Analysis of patient baseline characteristics in the intention-to-treat (ITT) population of the COLUMBUS and COMBI-v studies showed comparability in: median age (56.5 and 54.5 years, respectively), sex distribution (proportion of men 59.9% and 59%, respectively); proportion of patients with an ECOG score of 0/1 (100% in both trials); proportion of patients with metastatic stages M1c (64.1% and 63%, respectively); proportion with LDH greater than the upper limit of normal at baseline (28.6% and 33%,

respectively); the proportion of patients with a number of metastatic sites higher than, or equal to, three (45.5% and 33%, respectively). Populations in both studies consisted exclusively of patients with BRAF mutation. This analysis highlighted the similarity in baseline characteristics in the COLUMBUS and Combi-v study populations.

COLUMBUS and Comvi-v trials were found to be broadly similar in terms of study design (open-label) and patient inclusion criteria, as regards mutation status, performance status and prior therapy. The only notable difference was that COMBI-v allowed crossover from vemurafenib to Dabra+Tram after the first preliminary analysis (pre-specified in protocol), whereas the COLUMBUS trial did not permit crossover.

C.1.2 Risk of bias

The methodological quality of the studies included from the systematic review was assessed using the criteria for methodological quality as specified by the Cochrane Risk of Bias tool [4] and investigated the presence and extent of the biases that could affect study quality. Possible biases considered in this analysis were as follows:

- Randomisation: Was the method used to generate random allocations adequate?
- Allocation concealment: Was the allocation adequately concealed?
- Baseline characteristics: Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Blinding: Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Attrition: Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Outcomes: Is there any evidence to suggest that the authors measured more outcomes than they reported?
- ITT: Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Responses to the questions were categorised as: high risk (red), low risk (green), and unclear risk of bias (yellow). A table summarising the risk of bias in the studies included in the network is shown below.

Results of the quality assessment overall suggest low risk of bias; however, high risk of bias was observed in terms of allocation concealment and blinding as COLUMBUS and COMBI-v are open-label studies. Please note that as per Cochrane Risk of Bias tool [4], allocation concealment refers to “inadequate concealment of allocations prior to assignment” or “in advance, or during, enrolment”.

Table 1: Risk of bias in included studies in the ITC

Study	Randomisation	Allocation concealment	Baseline characteristics	Blinding	Attrition	Outcomes	ITT
COLUMBUS							
COMBI-v							

Abbreviations: ITT, intention to treat

C.2 General description of comparative analysis evidence synthesis method

The simple Bucher method [44] is recommended when there are paths between each node but each comparison has only been made in one study and therefore no pairwise meta-analysis is possible.

A summary of the data inputs used for the ITC are outlined in Table C.1.

Table C.2: Summary of data used in ITC

Outcome	Enco+Bini 450 vs. vemurafenib (COLUMBUS)	Source	Dabra+Tram vs. vemurafenib (COMBI-v)	Source
OS, HR (95% CI)	0.61 (0.47, 0.79)	Dummer OS 2018 [45]	0.68 (0.56, 0.83)	Dabrafenib and Trametinib SmPC [46,47]
Any grade 3-4 AEs, n/N (%)	Enco+Bini 450: 111/192 (57.8) Vemurafenib: 118/186 (63.4)	Dummer et al. 2018 [5]	Dabra+Tram: 200/350 (57.1) Vemurafenib: 225/349 (64.5)	Robert 2016 ESMO [48]
Discontinuation due to AEs, n/N (%)	Enco+Bini 450: 24/192 (12.5) Vemurafenib: 31/186 (16.7)	Dummer et al. 2018 [5]	Dabra+Tram: 57/350 (16.3) Vemurafenib: 54/349 (15.5)	Robert 2016 ESMO [48]
All SAEs, n/N (%)	Enco+Bini 450: 66/192 (34.4) Vemurafenib: 69/186 (37.1)	Dummer et al. 2018 [5]	Dabra+Tram: 131/350 (37.4) Vemurafenib: 122/349 (35.0)	Clincialtrials.gov [49]
PFS (investigator), HR (95% CI)	0.49 (0.37, 0.64)	Dummer et al. 2018 Supplementary appendix [5]	0.61 (0.51, 0.73)	Robert 2016 ESMO [48]
Overall response rate (investigator), n/N (%)	Enco+Bini 450: 145/192 (75.5) Vemurafenib: 94/191 (49.2)	Dummer OS 2018 [45]	Dabra+Tram: 236/352 (67) Vemurafenib: 187/352 (53)	Robert 2016 ESMO [48]
Duration of response (investigator), Median (95% CI)	Enco+Bini 450: 16.2 months (11.1, 24.1) Vemurafenib: 7.7 months (5.8, 11.0) Difference (SE): 8.5 (3.57)	Dummer OS 2018 [45]	Dabra+Tram: 13.8 (11.3, 17.7) Vemurafenib: 7.9 (7.4, 9.3) Difference (SE): 5.9 (1.70)	Robert 2016 ESMO [48]
EQ-5D utility score pre-progression, Mean utility score (SE)	[redacted]	COLUMBUS post-hoc analyses [51]	Dabra+Tram: 0.8409 (0.0040) Vemurafenib: 0.7502 (0.0090)	Grob 2015 [30]; NICE TA396 [52]

	[redacted]		Mean difference (SE): 0.0907 (0.009849)	
DCFB EQ-5D utility score (Week 32), DCFB (SE)	[redacted]	COLUMBUS post-hoc analyses [51]	Dabra+Tram vs. Vemurafenib: 0.10 (0.02)	Grob 2015 [30]
DCFB EQ-5D utility score (at disease progression), DCFB (SE)	[redacted]	COLUMBUS post-hoc analyses [51]	Dabra+Tram vs. Vemurafenib: 0.11 (0.03)	Grob 2015 [30]

Abbreviations: AE(s): adverse event(s); BIRC: Blinded Independent Review Committee; CI: confidence interval; DT: Dabra+Tram; EB: Enco+Bini 450; DCFB: difference in change from baseline; EMA: European Medicines Agency; OS: overall survival; HR: hazard ratio; ITC: indirect treatment comparison; PFS: progression-free survival; MAA: Marketing Authorisation Application; SE: standard error; SmPC: summary of product characteristics; V: vemurafenib

Notes: All efficacy outcomes for COLUMBUS are based on November 2017 data cut-off with the exception of PFS which is based on published PFS (per investigator) from the May 2016 data-cut; all safety outcomes for COLUMBUS are based on May 2016 data cut-off, all HRQoL outcomes for COLUMBUS are based on the May 2016 data cut-off

C.3 Model software and methods

The analyses to be conducted consisted of both continuous and binary outcomes. The key efficacy outcomes OS and PFS were analysed using log transformed HR and corresponding standard errors (SE) from each trial, assuming a normal distribution. Overall response rate and discontinuation due to AE were analysed as binary outcomes, using OR and corresponding SE from each trial, assuming a binomial distribution.

Bucher method analyses were conducted in Microsoft Office Excel as described by Bucher et al. 1997 [53]. Some of the advantages of using the Bucher method are described in section 2.1 in the ITC methods document published by the Canadian Agency for Drugs and Technologies in Health [54].

Indirect comparisons results are presented in the form of a table for all outcomes of interest, presenting the appropriate outcome measure with associated 95% CIs and p-value.

C.4 Effect modification

Fixed effects models were fitted. Fixed effects models make the assumption that each study is estimating the same treatment effect, with variability induced by sampling error alone. Conversely, by assuming that the trial-specific treatment effects come from a common distribution, a random effects model takes into account between-study heterogeneity, therefore producing wider CIs. In the present analysis, however, the networks are weak, consisting two RCTs in just a few links, thus a fixed effects model is more appropriate.

Meta-regression is an method that can be used to adjust for differences in study level effect modifiers, but in the present analysis it is not feasible due to the limited data availability (one study per comparison for most treatments, two in one treatment) [55].

C.5 Analysis assumptions

A number of assumptions were made and approaches adopted for conducting evidence synthesis:

- For clinical outcomes from the COLUMBUS trial, the November 2017 data cut was used fro efficacy outcomes, November 2016 data cut was used for safety outcomes and May 2016 data-cut for HRQoL outcomes
- Wherever available, the most recent, mature data for outcomes of interest from COMBI-v were used in an effort to minimise uncertainty; it is acknowledged that this approach entails use of data from different timepoints across included studies.
- Only doses approved in marketing authorisations were included in the decision set as other doses were deemed irrelevant for the purposes of health technology assessment and wider market access and reimbursement.

Appendix D. Summary of Product Characteristics (SmPC) & EPARs

D.1 SmPC: Encorafenib

Please click on the icon below to access the SmPC for encorafenib

Braftovi_SmPC.pdf

D.2 SmPC: Binimetinib

Please click on the icon below to access the SmPC for binimetinib.

Mektovi_SmPC.pdf

D.3 EPARs

Please click on the respective icons below to access the EPARs for encorafenib and binimetinib respectively.

Braftovi-EAPR-public-assessment-report

Mektovi-EPAR-public-assessment-report

References

[1] EMA. European public assessment reports. 2018.
[2] Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U, ESMO Guidelines Committee. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol 2015;26 Suppl 5:v126-132. doi:10.1093/annonc/mdv297.
[3] NICE. User guide for the cost comparison company evidence submission template. 2017.
[4] Cochrane Handbook for Systematic Reviews of Interventions n.d. http://handbook-5-1.cochrane.org/ (accessed October 6, 2017).
[5] Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018;0. doi:10.1016/S1470-2045(18)30142-6.
[6] Dummer R, Ascierto PA, Gogas H, Arance AM, Mandalà M, Liszkay G, et al. Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma. J Clin Oncol 2018;36:9504–9504. doi:10.1200/JCO.2018.36.15_suppl.9504.
[7] Gogas H, Dummer R, Ascierto PA, Arance AM, Mandalà M, Liszkay G, et al. Adverse events of special interest in the phase 3 COLUMBUS study. J Clin Oncol 2018;36:9504.
[8] Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30–9. doi:10.1056/NEJMoa1412690.
[9] Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroyakovskiy D, et al. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D)+ trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. Ann Oncol n.d.;27(suppl_6):LBA40.
[10] Long GV, Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol Off J Eur Soc Med Oncol 2017;28:1631–9. doi:10.1093/annonc/mdx176.
[11] Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371:1877–88. doi:10.1056/NEJMoa1406037.
[12] Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. The Lancet 2015;386:444–51. doi:10.1016/S0140-6736(15)60898-4.
[13] Long GV, Eroglu Z, Infante J, Patel S, Daud A, Johnson D. B, et al. Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma who received dabrafenib combined with trametinib. J Clin Oncol 2018;36:667–73.
[14] Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 Mutations. N Engl J Med 2012;367:1694–703. doi:10.1056/NEJMoa1210093.
[15] Latimer NR, Amonkar MM, Stapelkamp C, Sun P. Adjusting for confounding effects of treatment switching in a randomized phase II study of dabrafenib plus trametinib in BRAF V600+ metastatic melanoma. Melanoma Res 2015;25:528–536. doi:10.1097/CMR.0000000000000193.
[16] Long GV, Weber JS, Infante JR, Kim KB, Daud A, Gonzalez R, et al. Overall survival and durable responses in patients with BRAF V600–mutant metastatic melanoma receiving dabrafenib combined with trametinib. J Clin Oncol 2016;34:871–8. doi:10.1200/JCO.2015.62.9345.
[17] Ascierto PA, McArthur GA, Dréno B, Atkinson V, Liszkay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17:1248–60. doi:10.1016/S1470-2045(16)30122-X.

[18] Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma. N Engl J Med 2014;371:1867–76. doi:10.1056/NEJMoa1408868.
[19] Dréno B, Ribas A, Larkin J, Ascierto PA, Hauschild A, Thomas L, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. Ann Oncol Off J Eur Soc Med Oncol 2017;28:1137–44. doi:10.1093/annonc/mdx040.
[20] Hauschild A, Grob J-J, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. The Lancet 2012;380:358–65. doi:10.1016/S0140-6736(12)60868-X.
[21] Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. An update on BREAK-3, a phase III, randomized trial: Dabrafenib (DAB) versus dacarbazine (DTIC) in patients with BRAF V600E-positive mutation metastatic melanoma (MM). J Clin Oncol 2013;31:9013–9013. doi:10.1200/jco.2013.31.15_suppl.9013.
[22] Latimer NR, Abrams KR, Amonkar MM, Stapelkamp C, Swann RS. Adjusting for the Confounding Effects of Treatment Switching - The BREAK-3 Trial: Dabrafenib Versus Dacarbazine. The Oncologist 2015;20:798–805. doi:10.1634/theoncologist.2014-0429.
[23] Chapman PB, Robert C, Larkin J, Haanen JB, Ribas A, Hogg D, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. Ann Oncol Off J Eur Soc Med Oncol 2017;28:2581–7. doi:10.1093/annonc/mdx339.
[24] Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. N Engl J Med 2011;364:2507–16. doi:10.1056/NEJMoa1103782.
[25] McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014;15:323–32. doi:10.1016/S1470-2045(14)70012-9.
[26] Ugurel S, Röhmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies–update 2017. Eur J Cancer 2017;83:247–57. doi:10.1016/j.ejca.2017.06.028.
[27] Array BioPharma Inc. COLUMBUS: A 2-part phase III randomized, open label, multicenter study of LGX818 plus MEK162 versus vemurafenib and LGX818 monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma. 2017.
[28] Papaioannou D, Brazier J, Paisley S. NICE DSU Technical Support Document 9: The identification, review and synthesis of health state utility values from the literature. 2010.
[29] Gogas H, Dummer R, Ascierto PA, Mandala M, Liszkay G, Garbe C, et al. Quality-of-Life (QoL) in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant Melanoma. Ann Oncol 2017;28 (Suppl_5):v428–48.
[30] Grob JJ, Amonkar MM, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol 2015;16:1389–98.
[31] Grob JJ, Amonkar M, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. COMBI-v: Health-related quality of life (HRQoL) impact of the combination of dabrafenib and trametinib (D+T) vs vemurafenib (V) in patients with BRAF V600 metastatic melanoma (MM). Eur J Cancer 2015;51:S682–3.
[32] Schadendorf D, Amonkar MM, Stroyakovskiy D, Levchenko E, Gogas H, de Braud F, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. Eur J Cancer 2015;51:833–40.
[33] Robert C, Schadendorf D, Long GV, Stroyakovskiy D, Levchenko E, Chiarion-Sileni V, et al. Analysis of patient-reported outcomes by disease progression status in patients (pts) with BRAF V600-mutant metastatic melanoma in the COMBI-d and COMBI-v trials. Ann Oncol Conf 41st Eur Soc Med Oncol Congr ESMO 2016;27.
[34] Grob JJ, Robert C, Long GV, Stroyakovskiy D, Levchenko E, Chiarion-Sileni V, et al. Health-related quality-of-life (HRQOL) impact of dabrafenib (D) and trametinib (T) vs BRAF inhibitor (BRAFi)

monotherapy by lactate dehydrogenase (LDH) in patients (pts) with BRAF V600-mutant melanoma. Ann Oncol Conf 41st Eur Soc Med Oncol Congr ESMO 2016;27.
[35] Dreno B, Bartley K, Ascierto PA, Atkinson V, Liszkay G, Maio M, et al. Quality-of-life (QOL) assessment in patients (pts) with metastatic melanoma receiving vemurafenib (V) and cobimetinib (C). J Clin Oncol Conf 2015;33.
[36] Dreno B, Larkin J, McArthur G, Maio M, Demidov L, Park E, et al. Characterization of responders to cobimetinib (C) and vemurafenib (V) in patients (Pts) with BRAF-mutated metastatic melanoma (MM) in the coBRIM study. Pigment Cell Melanoma Res 2017;30 (1):93–4.
[37] Dreno B, Ascierto PA, Atkinson V, Liszkay G, Maio M, Mandala M, et al. Health-related quality of life impact of cobimetinib in combination with vemurafenib in patients with advanced or metastatic BRAFV600 mutation-positive melanoma. Br J Cancer 2018;118:777–84.
[38] Grob J, Algarra SM, Amonkar MM, Demidov LV, Goodman VL, Grotzinger K, et al. Dabrafenib vs dacarbazine (DTIC) in patients with BRAF V600+ advanced and metastatic melanoma in BREAK-3: Quality of life (QOL) analysis. Pigment Cell Melanoma Res 2013;26 (1):152.
[39] Grob JJ, Amonkar MM, Martin-Algarra S, Demidov LV, Goodman V, Grotzinger K, et al. Patient perception of the benefit of a BRAF inhibitor in metastatic melanoma: quality-of-life analyses of the BREAK-3 study comparing dabrafenib with dacarbazine. Ann Oncol 2014;25:1428–36.
[40] NICE. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma. Technology appraisal guidance (TA 396) 2016.
[41] NICE. Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Technology appraisal guidance (TA 414) 2016.
[42] NICE. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation‑positive melanoma. Technology appraisal guidance (TA 321) 2014.
[43] Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC Med 2013;11:159. doi:10.1186/1741-7015-11-159.
[44] Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683–91.
[45] Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018;19:1315–27. doi:10.1016/S1470-2045(18)30497-2.
[46] Novartis Europharm Ltd. Summary of product characteristics: Dabrafenib (Tafinlar) 50mg and 75mg capsules. 2017.
[47] Novartis Europharm Ltd. Summary of product characteristics: Trametinib (Mekinist) 0.5mg and 2mg tablets. 2017.
[48] Robert,Caroline. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. ESMO, Copenhagen 2016.
[49] ClinicalTrials.gov. Dabrafenib Plus Trametinib vs Vemurafenib Alone in Unresectable or Metastatic BRAF V600E/K Cutaneous Melanoma (COMBI-v). NCT01597908. 2018.
[50] Array BioPharma Inc. Efficacy update CMEK162B2301: 7 November 2017 data cut-off. 2018.
[51] Laboratoires Pierre Fabre. COLUMBUS: Post-hoc QoL analyses report [commercial in confidence]. 2018.
[52] NICE. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma [TA396]. Final Appraisal Determination. ERG Report. 2016.
[53] Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683–91.
[54] Wells, GA, Sultan, SA, Chen, L, Khan, M, Coyle, D. Quality assessment tools project report. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.
[55] Dias S, Welton N, Sutton A, Caldwell D, Lu G, Ades A. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2010.

Protokol for vurdering af den kliniske merværdi af encorafenib i kombination med binimetinib til ikke-resektabel eller metastatisk modermærke-kræft med BRAF V600 mutation

Handelsnavn	Braftovi i kombination med Mektovi
Generisk navn	Encorafenib i kombination med binimetinib
Firma	Pierre Fabre
ATC-kode	
Virkningsmekanisme	Encorafenib: RAF-kinase inhibitor Binimetinib: MEK 1 og MEK 2 inhibitor
Administration/dosis	Encorafenib 450 mg 1 gang dagligt, oral tablet behandling. Binimetinib 45 mg 2 gange dagligt, oral tablet behandling.
Forventet EMA-indikation	Encorafenib i kombination med binimetinib til behandling af voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	11.09.2018 11.09.2018 26790 1.0

Indhold

Forkortelser

AE:	*Adverse Events (uønskede hændelser)*
CI:	Konfidensinterval
EMA:	*European Medicines Agency*
GRADE:	System til vurdering af evidens *(Grading of Recommendations Assessment, Development and Evaluation)*
HR:	*Hazard Ratio*
LDH:	Lactatdehydrogenase
PFS:	*Progression Free Survival*
MAP	Mitogen Aktiveret Protein
MAPK:	Mitogen Aktiveret Protein Kinase
OR:	*Odds Ratio*
ORR	*Overall Response Rate*
OS	*Overall Survival*
RR:	Relativ Risiko
QOL:	*Quality of Life*
UNL:	*Upper Normal Limit*

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af encorafenib i kombination med binimetinib som mulig standardbehandling af patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation. I protokollen angives en definition af populationer, komparatorer og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende encorafenib i kombination med binimetinib modtaget 16.04.2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af encorafenib i kombination med binimetinib sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem encorafenib i kombination med binimetinib og komparatoren dabrafenib i kombination med trametinib af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

2 Baggrund

Modermærkekræft opstår i melanocytter i modermærker og er blandt de hyppigste kræftformer i Danmark, den 4. hyppigste kræftform hos kvinder og den 5. hyppigste hos mænd. Ifølge Dansk Modermærkekræft Gruppes (DMG) årsrapport blev der i 2016 registreret 2.778 nye tilfælde i Danmark. Sygdommen optræder hovedsageligt hos personer i aldersgruppen 40 til 70 år, men helt unge rammes også [1].

Sygdommens stadie grupperes efter TNM-klassifikationen: Tumor, Node (lymfeknude) og Metastase. Disse parametre siger noget om hvor fremskreden primær tumor er, i form af tykkelsen af tumor, status for spredning (metastaser) til nærmeste lymfeknuderegion (N0 for ingen spredning, N3 for alvorlig spredning) og status for fjernmetastaser, M0 for ingen fjernmetastaser og M1c for alvorlige spredning til indre organer [2,3]. Stadieinddeling af modermærkekræft baseres på disse parametre.

Prognosen for modermærkekræft er generelt god, da de fleste tilfælde opdages tidligt [3,4]. Overlevelsen forventes at stige de kommende år på grund af de tilkomne behandlingsmuligheder. Prognosen er bedre, hvis der kun er spredning til huden eller til lymfeknuder fjernt fra tumorstedet (M1a), sammenlignet med spredning til indre organer (M1b, M1c eller M1d).

Den primære behandling er operation. Trods operation vil nogle patienter udvikle metastatisk modermærkekræft og være kandidater til medicinsk behandling (ca. 330 nye patienter pr. år). Omkring 40-50 % af disse patienter har en BRAF-mutation. De organer, sygdommen hyppigst metastaserer til, er lymfeknuder, lunger, lever og hjerne, men også metastaser til knogler, knoglemarv, milt og andre organer, samt muskler og bindevæv ses. Forekomst af organmetastaser er generelt ensbetydende med en meget dårlig prognose [4]. For stadie IV patienter er der, baseret på danske upublicerede tal, en femårs-overlevelse (OS) på cirka 13 % for alle diagnosticerede med metastatisk melanom i 2012 [5].

BRAF-genet koder for B-Raf proteinet, som er en serin/threonin protein kinase, der aktiverer mitogen aktiveret protein kinase (MAPK) signalvejen. Omkring 40-50 % af alle modermærkekræftpatienter har aktiverende BRAF-mutationer, som resulterer i konstitutiv aktivering af MAPK signalvejen. Mutationen er forbundet med øget celleproliferation og dermed tumorvækst. Mutationsundersøgelsen foretages på

nuværende tidspunkt kun rutinemæssigt hos patienter med metastaser (regionalt eller fjernmetastaser) [6].

2.1 Nuværende behandling

Den foretrukne standardbehandling i Danmark af patienter med ikke-resektabel eller metastatisk modermærkekræft, uanset BRAF V600 mutationsstatus, er immunterapi i form af checkpoint hæmmere. Checkpoint hæmmere foretrækkes, fordi der er dokumenteret en langtidseffekt med disse, som ikke ses ved BRAF-kinasehæmmere i kombination med en MEK1 og MEK2 hæmmer. Dette afspejles også i opdaterede vejledninger fra internationale selskaber [7].

På baggrund af dette anvendes BRAF-kinasehæmmere i kombination med en MEK1 og MEK2 hæmmer primært i andenlinje. I Danmark består denne behandling af dabrafenib i kombination med trametinib [8]. Fagudvalget vurderer, at et estimat for potentielle kandidater til andenlinje behandling vil ligge på omkring 55-60 patienter.

BRAF-kinasehæmmere i kombination med en MEK1 og MEK2 hæmmer finder dog både i Danmark og international anvendelse i førstelinje til patienter med BRAF-mutation med følgende karakteristika:

- patienter med symptomatiske hjernemetastaser
- laktat-dehydrogenase LDH > ULN*2 (øvre normal grænse)
- stor tumorbyrde
- hurtigvoksende sygdom
- symptomatisk sygdom
  eller
- relative kontraindikationer til immunterapi (f.eks. behandlingskrævende autoimmun sygdom)

Fagudvalget vurderer, at et estimat for potentielle kandidater til førstelinje behandling for hjernemetastaser og LDH > ULN*2 vil ligge på omkring 30-35 patienter [8]. Derudover vurderer fagudvalget, at et estimat for potentielle kandidater til førstelinje behandling med de øvrige karakteristika vil ligge på omtrent 20 - 25 patienter [5]. Dette afspejles ligeledes i opdaterede vejledninger fra internationale selskaber [7].

2.2 Encorafenib i kombination med binimetinib

Encorafenib er en selektiv hæmmer af BRAF kinasen og hæmmer MAPK-signalvejen hos BRAF V600E, V600D og V600K muterede melanom celler, beskrevet i afsnit 2 [9].

Binimetinib er en selektiv hæmmer af MEK1 og MEK2, som aktiverer mitogen aktiveret protein (MAP) [9].

Farmakokinetisk adskiller encorafenib sig med en dissociationshalveringstid omkring 10 gange længere (> 30 timer) sammenlignet med de øvrige BRAF-kinase inhibitorer. Prækliniske studier indikerer, at denne faktor kan forstærke anti-tumor aktiviteten [9].

Den forventede indikation for encorafenib i kombination med binimetinib gælder for patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation.

Den ansøgte indikation er baseret på COLUMBUS studiet [9], hvor encorafenib (450 mg én gang dagligt) i kombination med binimetinib (45 mg to gange dagligt) er sammenlignet med encorafenib alene (300 mg én gang dagligt) eller BRAF-kinase inhibitoren vemurafenib alene (960 mg to gange dagligt) [9]. Behandlingsvarigheden er frem til progression, død eller ophør grundet bivirkninger.

3 Kliniske spørgsmål

3.1 Klinisk spørgsmål 1

1. *Hvilken klinisk merværdi tilbyder encorafenib i kombination med binimetinib sammenlignet med dabrafenib i kombination med trametinib til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinje behandling med en BRAF-MEK hæmmer?*

Population
Voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til førstelinjebehandling med BRAF-MEK hæmmere, som beskrevet i afsnit 2.1.

Intervention
Oral tablet encorafenib, 450 mg 1 tablet daglig, i kombination med oral tablet binimetinib, 45 mg 1 tablet 2 gange dagligt.

Komparator
Oral tablet dabrafenib, 150 mg 1 tablet 2 gange dagligt, i kombination med oral tablet trametinib, 2 mg 1 tablet dagligt.

Effektmål
Tabel 1 i afsnit 3.3 opsummerer de valgte effektmål, deres vigtighed, mindste kliniske relevante forskel og kategori.

3.2 Klinisk spørgsmål 2

2. *Hvilken klinisk merværdi tilbyder encorafenib i kombination med binimetinib sammenlignet med dabrafenib i kombination med trametinib til patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinje behandling med en BRAF-MEK hæmmer?*

Population
Voksne patienter med ikke-resektabel eller metastatisk modermærkekræft med BRAF V600 mutation, som er kandidater til andenlinjebehandling med BRAF-MEK hæmmere, som beskrevet i afsnit 2.1.

Intervention
Oral tablet encorafenib, 450 mg 1 tablet daglig, i kombination med oral tablet binimetinib, 45 mg 1 tablet 2 gange dagligt.

Komparator
Oral tablet dabrafenib, 150 mg 1 tablet 2 gange dagligt, i kombination med oral tablet trametinib, 2 mg 1 tablet dagligt.

Effektmål
Tabel 1 i afsnit 3.3 opsummerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.

3.3 Valg af effektmål

Tabel 1 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori. Nedenstående tabel gælder for begge kliniske spørgsmål.
For alle effektmål ønskes både absolutte og relative værdier, jævnfør ansøgningsskemaet. For de relative værdier vurderes den kliniske relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 1

Effektmål*	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Overlevelse (OS)	Kritisk	Overlevelse	Median OS eller OS rate ved 1 år	En forskel på 3 måneder En forskel på 10 %- point
Bivirkninger	Kritisk	Alvorlige symptomer og bivirkninger	Andel af patienter, som oplever en eller flere bivirkninger grad 3-4	En forskel på 10 %-point
			Andel af patienter, med behandlingsophør som følge af bivirkninger	En forskel på 5 %-point
			Kvalitativ gennemgang af bivirkningstyperne med henblik på at vurdere alvorlighed, håndterbarhed og tyngde af bivirkningerne	Narrativ vurdering
Progression free survival (PFS)	Vigtig	Alvorlige symptomer og bivirkninger	Median PFS	En forskel på 3 måneder
Livskvalitet	Vigtig	Helbredsrelateret livskvalitet	Ændring over tid i identiske livskvalitetsspørgeskemaer	Forskel i ændring svarende til de validerede mindste klinisk relevante forskelle for de involverede livskvalitets-Spørgeskemaer,beskrevet nedenfor
Overall response rate (ORR)	Vigtig	Alvorlige symptomer og bivirkninger	Andel af patienter, der opnår respons	En forskel på 10 %-point

Duration of response	Vigtig	Alvorlige symptomer og bivirkninger	Median DoR	En forskel på 2 måneder
Overall response rate (ORR) hjernemetastaser	Vigtig	Alvorlige symptomer og bivirkninger	Andel af patienter, der opnår respons	En forskel på 10 %-point

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Den samlede kliniske merværdi af encorafenib i kombination med trametinib sammenlignet med dabrafenib i kombination med trametinib baseres på en tidshorisont på længst mulig opfølgningstid. Tidsangivelser i tabellen er defineret på baggrund af den foreløbige ansøgning.

Kritiske effektmål

Overlevelse

Forbedret samlet overlevelse betragtes som guldstandard blandt effektmål i onkologiske studier. Overlevelse defineres som tiden fra behandlingsstart til død, uafhængigt af årsag.

Fagudvalget vurderer, at en forskel på 3 måneder i median OS eller 10 %-point i OS rate ved 1 år mellem encorafenib i kombination med binimetinib og dabrafenib i kombination med trametinib, er klinisk relevant.

For at redegøre for en mulig efterfølgende cross-over effekt, ønsker fagudvalget en opgørelse af efterfølgende behandling efter ophør af en BRAF-MEK hæmmer i førstelinje behandling (klinisk spørgsmål 1).

Bivirkninger

Fagudvalget finder det relevant at belyse bivirkninger (adverse reactions (AR)) grad 3-4 samt behandlingsophør på grund af bivirkninger (AR), da det belyser hvorvidt encorafenib i kombination med binimetinib tolereres sammenlignet med dabrafenib i kombination med trametinib. Bivirkninger suppleres med en kvalitativ gennemgang.

Bivirkninger grad 3-4 (AR))

Det er fagudvalgets betragtning, at andelen af patienter, som oplever en eller flere bivirkninger grad 3-4 i henhold til National Cancer Institute CTCAE, version 4.0 [10], er relevant for vurderingen. Mindste klinisk relevante forskel sættes til 10 %-point mellem encorafenib i kombination med binimetinib sammenlignet med dabrafenib i kombination med trametinib.

Behandlingsophør på grund af bivirkninger

Behandlingsophør på grund af bivirkninger reflekterer, hvorvidt encorafenib i kombination med binimetinib tolereres sammenlignet med dabrafenib i kombination med trametinib. Behandlingsophør på grund af alvorlige bivirkninger ønskes oplyst og fagudvalget vurderer, at en forskel på 5 %-point mellem grupperne er klinisk relevant. Fastlæggelsen af den mindste klinisk relevante forskel afspejler fagudvalgets kliniske

erfaring med dabrafenib i kombination med trametinib i metastatisk behandling, hvor ophør grundet bivirkninger er velkendt.

Kendte bivirkninger
Fagudvalget ønsker derudover en kvalitativ gennemgang af bivirkningstyperne (grad 3-4) forbundet med encorafenib i kombination med binimetinib med henblik på at vurdere typer, håndterbarhed samt reversibilitet af bivirkningerne. Fagudvalget ønsker at få belyst antallet af patienter, der bliver dosisreduceret grundet bivirkninger. Fagudvalget lægger særligt vægt på bivirkningerne: pyrexi, fototoxicitet, samt påvirkning af hjertets pumpefunktion. På baggrund af kendt interaktion mellem BRAF/MEK-hæmmere og stråleterapi ønsker fagudvalget at få belyst interaktionen mellem encorafenib/binimetinib og strålebehandling set i lyset af den længere halveringstid med encorafenib. Ansøger bedes derfor bidrage med bivirkningsdata fra både kliniske studier samt produktresuméerne for lægemidlerne.

Vigtige effektmål

Progressionsfri overlevelse (PFS)

PFS anvendes til vurdering af sygdomsprogression og defineres som tiden fra studierandomisering til første dokumentation af progression i henhold til Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [11] eller dødsfald. PFS er et standard primært effektmål for metastaserende kræft i de fleste randomiserede kliniske studier og anvendes til tider af EMA som et surrogatendepunkt for OS, hvis der ikke foreligger valide OS-data.

Fagudvalget vurderer, at en forskel på 3 måneder i median PFS mellem encorafenib i kombination med binimetinib og dabrafenib i kombination med trametinib, er klinisk relevant.

Livskvalitet

Livskvalitet kan måles med flere forskellige instrumenter. Fagudvalget vurderer, at følgende validerede spørgeskemaer er relevante:

European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30 (EORTC-QLQ-C30) [12] består af fem funktionsskalaer, tre symptomskalaer og en "global" livskvalitetsskala. Der anvendes en scoringsskala fra 0-100. En høj score på de fem funktionsskalaer repræsenterer et højt/positivt funktionsniveau. En høj score for global helbredsstatus repræsenterer høj livskvalitet, mens en høj score på de tre symptomskalaer repræsenterer høj forekomst af symptomer/problemer [10]. En lille ændring er defineret som en ændring på 5-10 point, en moderat ændring er 10-20 point, og en stor ændring er > 20 point. Den mindste klinisk relevante forskel baserer sig på en lille ændring defineret som $\geq$ 5 point.

EQ-5D spørgeskemaet er et velvalideret generisk spørgeskema, som anvendes til vurdering af helbredsrelateret livskvalitet (EuroQol Group). Spørgeskemaet består af fem dimensioner (bevægelighed, personlig pleje, sædvanlige aktiviteter, smerte/ubehag og angst/depression). Spørgeskemaet indeholder desuden en visuel analog skala (VAS), der får fra 0 (værst tænkelige helbred) til 100 (bedst tænkelige helbred). Den mindste kliniske relevante forskel er baseret på de britiske værdier fra Pickard et al. Fagudvalget læner sig op ad denne definition og betragter en forskel på ≥ 0,08 i EQ-5D

index score og ≥ 7 point i EQ-5D visuel analog skala mellem encorafenib i kombination med binimetinib og komparator er klinisk relevant [13,14].

Overall response rate (ORR)

ORR anvendes til belysning af behandlingsrespons, og er defineret som andelen af patienter som opnår delvist eller komplet respons. Fagudvalget vurderer, at tumorreduktion medfører en periode med forbedring eller ingen forværring af symptomer. Responsraten vurderes derfor at være et vigtigt effektmål.

Fagudvalget vurderer, at en forskel på 10 %-point i andel af patienter, der oplever respons mellem encorafenib i kombination med binimetinib og dabrafenib i kombination med trametinib, er klinisk relevant.

Duration of response (DoR)

DoR beskriver tiden fra første dokumenterede respons (bekræftet komplet respons eller delvis respons) til datoen for progression eller død, som følge af modermærkekræft.

Fagudvalget vurderer, at en forskel på 2 måneder i median DoR mellem encorafenib i kombination med binimetinib og dabrafenib i kombination med trametinib,er klinisk relevant.

CNS metastaser Overall response rate (ORR)

Fagudvalget ønsker at få belyst en effekt på specifikt hjernemetastaser. ORR anvendes til belysning af behandlingsrespons. Fagudvalget vurderer, at tumorreduktion medfører en periode med forbedring eller ingen forværring af symptomer. Responsraten vurderes derfor at være et vigtigt effektmål.

Fagudvalget vurderer, at en forskel på 10 %-point i andel af patienter, der oplever respons på hjernemetastaser mellem encorafenib i kombination med binimetinib og dabrafenib i kombination med trametinib, er relevant.

4 Litteratursøgning

Databaser for søgningen

Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgetermer

Søgningen skal inkludere det generiske navn og handelsnavnet for både det aktuelle lægemiddel og dets komparator(er), som kombineres med termer for indikationen.

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes.

Lægemiddel/komparator(er)	Indikation
encorafenib, Braftovi, binimetinib, Mektovi	modermærkekræft
dabrafenib, Tafinlar, trametenib, Mekinist	

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

Kriterier for udvælgelse af litteratur

Der ekskluderes først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder om, hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier: Andre studiedesign end randomiserede kontrollerede studier ekskluderes, fase I og fase IIa-studier ekskluderes. Derudover ekskluderes studier med andre populationer end de valgte og studier, som ikke rapporterer mindst et af de kritiske eller vigtige effektmål.

Vurderingen af klinisk merværdi baseres på data fra publicerede fuldtekstartikler og data fra EMAs EPAR – Public assessment report. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data og data fra f.eks. abstracts kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige for at sikre en fair sammenligning. Data skal i så fald stamme fra de forsøg, hovedpublikationerne rapporterer fra, og ansøger skal acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. klinisk merværdi.

5 Databehandling/analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængeligt for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risiko reduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end et sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans. Såfremt en metaanalyse vil være relevant ønskes en vurdering af, om studierne er homogene nok til sammenligning.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

6 Andre overvejelser

7 Referencer

1. Danish Melanoma Group. Dansk Melanom Database. National Årsrapport 2016. Annual report. 2016.
2. American Cancer Society. Melanoma of the Skin Staging. 2009.
3. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long G V, Ross MI, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(6):472–92.
4. Rådet for Anvendelse af Dyr Sygehusmedicin (RADS). RADS Baggrundsnotat for metastaserende malignt melanom. 2016.
5. Dansk Melanom Gruppe. Danish Metastatic Melanoma Database. 2017.

6. RADS Baggrundsnotat for metastaserende malignt melanom. København; 2016.

7. Sullivan RJ, Atkins MB, Kirkwood JM, Agarwala SS, Clark JI, Ernstoff MS, et al. An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: Version 2.0. J Immunother Cancer. 2018;6(1):1–23.

8. Rådet for Anvendelse af Dyr Sygehusmedicin (RADS). RADS Behandlingsvejledning for metastaserende malignt melanom. København; 2016.

9. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):603–15.

10. National Cancer Institute Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Bd. 2009. 2010.

11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.

12. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.

13. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199–208.

14. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.

8 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende modermærkekræft

Formand	*Indstillet af*
Marco Donia Klinisk lektor, afdelingslæge, ph.d.	Lægevidenskabelige Selskaber
Medlemmer	*Udpeget af*
Adam Andrzej Luczak Overlæge	Region Nord
Trine Heide Øllegaard Afdelingslæge, ph.d	Region Midt
Lars Bastholt Overlæge	Region Syddanmark
Vurderet at udpegning ikke var relevant	Region Sjælland
Marco Donia	Region Hovedstaden
Niels Jessen Professor, overlæge	Dansk Selskab for Klinisk Farmakologi (DSKF)
Ingen udpegning	Dansk Selskab for sygehusapoteksledelse (DSS)
Mathilde Skaarup Larsen Overlæge, ph.d	Dansk Patologiselskab (DPAS)
Lisbet Rosenkrantz Hölmich Klinisk forskningslektor, overlæge, dr.med.	Dansk Selskab for Plastik- og Rekonstruktionskirurgi (DSPR)
Lisbet Rosenkrantz Hölmich	Dansk Melanom Gruppe (DMG)
Søren Chrestensen	Danske Patienter
Lene Ottesen	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Jette Østergaard Rathe (projekt- og metodeansvarlig) Charlotte Wulf Johansen (koordinator) Agla Jael Fridriksdottir (sundhedsvidenskabelig konsulent) Tenna Bekker (teamleder)